EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2026
EMA/CHMP/274515/2025 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enflonsia

International non-proprietary name: Clesrovimab

Procedure No. EMEA/H/C/006497/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ApaT	All participants as treated
CHD	congenital heart disease
CLD	chronic lung disease
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CSR	Clinical study report
CV	Coefficient of variation
DDI	Drug-drug interactions
DP	Drug substance
DS	Drug product
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic case report form
FAS	Full analysis set
Fc	Fragment crystallizable
hERG	Human Ether-a-go-go-Related Gene
ICU	Intensive care unit
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IM	intramuscular
IV	Intravenous
ISS	Integrated Summary of Safety
LRI	Lower respiratory infection
LRT	Lower respiratory tract
LRTI	Lower respiratory tract infection
MAA	Marketing authorization application
mAb	monoclonal antibody
MALRI	medically attended lower respiratory infection
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NP	Nasopharyngeal
PCR	polymerase chain reaction
PD	Pharmacodynamics
PDCO	Paediatric Committee (European Medicines Agency)
PFS	Pre-filled syringe
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
popPK	Population pharmacokinetics
PSP	Pediatric Study Plan
PT	Preferred term
QTc	Interval heartbeat
RSV	respiratory syncytial virus
SAE	serious adverse event
SOC	system organ class

Tmax	Time to maximum concentration
UR	Uncertainty range
URTI	Upper respiratory tract infection
Vc	Central volume of distribution
Vc/F	Apparent central volume of distribution
VL-AUC	Area under the viral load-time curve
Vp	Peripheral volume of distribution
Vp/F	Apparent peripheral volume of distribution
WONCBP	Women of non-childbearing potential
YTE	Substitutions in Fc region of RB1 to extend serum half-life

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 4 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Enflonsia, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

> *Clesrovimab Merck Sharp & Dohme is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.*
>
> *Clesrovimab Merck Sharp & Dohme should be used in accordance with official recommendations.*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, nonclinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0523/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

N/A

1.4.2. Derogation(s) from market exclusivity

N/A

1.4.3. New active Substance status

The applicant requested the active substance clesrovimab (MK-1654) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

During the development of MK-1654, the Applicant sought Scientific Advice from the EMA Scientific Advice Working Party (SAWP) four times. All aspects that were discussed critically during these advice procedures and are deviating from the final study designs will be discussed in the respective methods or result section and raised as OCs there.

Notably, the clinical development evolved over time and thus, does not entirely reflect plans that were discussed at the time EMA scientific advice was sought.

Date	**Reference**	**SAWP co-ordinators**
09/11/2017	EMEA/H/SA/3686/1/2017/PED/III	*Minne Casteels and Caroline Auriche*
27/06/2019	EMEA/H/SA/3686/1/FU/1/2019/PED/II	*Hans Ovelgönne and Mair Powel*
12/11/2020	EMEA/H/SA/3686/2/2020/I	*Nicolas Beix and Paolo Foggi*
22/06/2023	EMA/SA/0000132496	*Elisabeth Wischnitzki, Larissa Higgins and Anders Lignell*

2017: EMEA/H/SA/3686/1/2017/PED/III

The Scientific Advice pertained to the following aspects.

Non-clinical

Acceptability of nonclinical toxicology package supporting MAA.

Clinical

Acceptability of Phase 2b/Phase 3 development including dose selection, choice of population, primary endpoint, secondary endpoint and suitability of a palivizumab-controlled study in infants eligible for palivizumab to support MAA.

2019: EMEA/H/SA/3686/1/FU/1/2019/PED/II

The Scientific Advice pertained to the following aspects.

Clinical

Acceptability of pivotal Phase2b/Phase 3 study including design of the study, definition of RSV MALRI, choice primary endpoint, suitability of primary and secondary analysis based on rates of hospitalised cases of RSV MALRI, sampling for RT-PCR, extrapolation via PK bridging, suitability of a popPK model and analysis of the PK-PD relationship and choice of fixed dose to support MAA.

2020: EMEA/H/SA/3686/2/2020/I

The Scientific Advice pertained to the following aspects.

Quality

The Scientific Advice pertained to the following aspects.

Acceptability of Process 1 vs. Process 2 Comparability Plan; Acceptability of qualification plan for a replacement drug substance (DS) storage container closure system; Acceptability of introducing MK-1654 DP in a pre-filled syringe (PFS) presentation for commercial presentation in addition to a vial.

2023: EMA/SA/0000132496

The Scientific Advice pertained to the following aspects.

Quality

Finished product process performance qualification plan, analytical comparability plan to introduce new active substance and finished product manufacturing sites and to support a presentation change from vial to PFS, strategy to establish the shelf life of finished product in PFS.

Clinical

Acceptability of extrapolation of efficacy from the healthy preterm and full-term infants in PN004 to the palivizumab-eligible infants in PN007 in both RSV Season 1 and Season 2.

Paediatric development and pre-submission meeting

Paediatric development plans have been aligned on with EMA as follows:

> PIP, including a waiver for children from 2 years to <18 years of age, was initially agreed upon with the PDCO on 22-DEC-2020 and subsequently modified with an agreed number of participants from MK-1654-004 and MK-1654-007 to be included in the interim study reports in the initial MAA.

A pre-submission meeting was held in September 2024, where it was noted that the clinical development evolved since the scientific advice procedures (as mentioned above).

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Thalia Marie Estrup Blicher

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Gabriele Maurer

The application was received by the EMA on	4 November 2024
The procedure started on	28 November 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 February 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 March 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to	24 July 2025

the applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	02 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Enflonsia on	18 September 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	18 September 2025
The applicant informed the Agency about a revised dataset to be submitted. As a result, the Commission Decision process was put on hold while waiting for this information. The applicant submitted their response	15 December 2025
A new timetable adopted via written procedure	19 December 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	06 February 2026
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 February 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a revised positive opinion for granting a marketing authorisation to Enflonsia on	26 February 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Respiratory syncytial virus (RSV) is an enveloped RNA virus and the most common cause of bronchiolitis, LRTIs, and hospitalization in infants. All infants, including healthy infants born at term, are at risk for severe RSV LRTI with primary RSV infection in infancy.

2.1.2. Epidemiology and risk factors

Globally, based on 2019 worldwide population estimates, 33.0 million (UR: 25.4 to 44.6) episodes of RSV occur annually in children under 5 years of age, including 3.6 million (UR: 2.9 to 4.6) resulting in hospitalization; 39% of these hospitalizations occur in infants <6 months (Li et al 2022). Importantly, most infants (~65%) hospitalized with RSV infection have no predisposing risk factors and are

otherwise healthy. RSV is estimated to cause 28% of acute LRIs and 13% to 22% of deaths from acute LRIs in children under 5 years of age worldwide.

The virus has 2 strains (ie, RSV A and RSV B) that co-circulate during RSV season. Globally, children infected with RSV have a higher risk of subsequently developing chronic conditions such as allergic rhino-conjunctivitis, recurrent wheezing, and asthma.

Preterm infants, and those with underlying medical conditions, are predisposed to severe RSV infection. Children at increased risk of severe RSV disease include those born preterm, those born preterm with CLD, and infants with hemodynamically significant CHD. Infants born prematurely are at higher risk of severe RSV-associated outcomes as compared to term infants, have a median RSV-associated hospital length of stay of 2 to 17 days in the hospital, and up to 75% are admitted to ICU depending on gestational age. Studies have shown that infants born before 29 weeks have 2 to 4 times higher rates of RSV-associated hospitalization compared with later preterm infants. CLD was identified as the strongest risk factor (incidence rate ratio of 10.7; 95% CI: 8.4, 13.6) for RSV-associated hospitalization in a multivariate analysis adjusted for medical and demographic characteristics in children under 1 year of age.

Mortality associated with RSV infection is estimated at 101,400 (UR: 84,500 to 125,200) childhood deaths worldwide annually. The overwhelming majority of these deaths occur in low- and middle-income countries, where underreporting and at-home deaths are more common. Therefore, the number of deaths due to RSV worldwide may be even higher.

Impact in the EU

In the EU, an estimated 245,244 (95% CI: 224,688-265,799) RSV-associated hospitalizations occur every year in children <5 years of age, with most cases observed in children aged <1year (75%) followed by those aged 1 to 2 years of age (21%). The highest RSV-associated hospitalization rates (71.6 per 1000 population) are observed among the youngest age group (0 to 2 months of age), with rates decreasing for older children (38.9 per 1000 among those 3 to 5 months old, 17.6 per 1000 among 6 to 11 months old, 5 per 1000 among 12 to 35 months old and 1 per 1,000 among 36 to 59 months old). Overall, it is estimated that 10 of 1000 children aged 0 to 59 months living in the EU are hospitalized due to RSV every year. Approximately 60% of the estimated annual RSV-associated hospitalizations in children.

Seasonality

Due to seasonality, RSV disease typically occurs year-round in tropical climates and during the winter months in temperate climates. Due to the SARS-CoV-2 pandemic, which began in early 2020, the usual RSV seasonality was greatly disrupted with little or no RSV activity seen in most countries because of lockdowns and isolative measures. By 2023, the RSV activity reverted to pre-COVID-19 seasonality in most countries.

2.1.3. Biologic features, aetiology and pathogenesis

Respiratory syncytial virus (RSV) is an enveloped non-segmented negative-sense single stranded RNA virus that belongs to the family of *Paramyxoviridae.* Its name is derived from the large cells known as syncytia that form when infected cells fuse.

RSV replication initially occurs in the epithelial cells of the nasopharynx, from where it may spread into the lower respiratory tract.

2.1.4. Clinical presentation, diagnosis and prognosis

Respiratory syncytial virus LRTI is a potentially serious and life-threatening disease characterised by infection and inflammation of the alveoli and bronchioles. It is associated with necrosis and sloughing of the epithelium of the small airways, with oedema and increased secretion of mucus. This can lead to airway obstruction and a typical clinical picture of hyperinflation, atelectasis, and wheezing. It is most severe when the disease occurs in the first year of life associated with smaller airway diameter in infants. Known factors increasing the risk of hospitalisation with RSV include male sex, age under 6 months, crowding, siblings, and daycare exposure. Some infants with serious underlying comorbidities are at higher risk of severe disease, including prematurity, CLD, CHD, cystic fibrosis, neuromuscular conditions, Down syndrome, or immunocompromise. Lung immaturity, impaired vascular or pulmonary function, inability to clear secretions, or immunocompromise can all exacerbate the pathophysiology of RSV LRTI increasing the severity of the disease.

2.1.5. Management

Current therapies for the prevention of RSV in infants/children are:

• Synagis™ (generic name: palivizumab; MedImmune, acquired by AstraZeneca), a humanized prophylactic mAb directed against the RSV F protein, was approved in the US in June 1998 and in the EU in August 1999 for the prevention of serious LRT disease caused by RSV in infants and children with medical conditions that place them at risk of complications from RSV (eg, children born with a history of premature birth ≤35 weeks, children ≤2 years of age with CLD and CHD). Palivizumab is given by IM injection monthly during the RSV season.

• Abrysvo™ (generic name: RSV vaccine for injection; Pfizer), a vaccine containing RSV stabilized prefusion F proteins, was approved in the US in May 2023 and in the EU in August 2023 for prevention of RSV in infants through maternal immunization. The vaccine is administered between Weeks 32 to 36 of gestation in the US and between Weeks 24 and 36 of gestation in the EU.

• Beyfortus™ (generic name: nirsevimab; AstraZeneca), a human mAb with YTE substitutions, targeting antigenic Site Ø on the RSV F protein, received approval in the EU in October 2022 for prevention of RSV disease in infants in their first RSV season and in August 2024, for the prevention in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. In July 2023, nirsevimab received approval in the US 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.

The RSV prevention landscape is rapidly evolving. While the implementation of existing and preventative therapies is still being determined, reducing RSV infection, disease, and hospitalization in all infants, both healthy and those at increased risk, is of continued importance globally. To address potential resistance development, it is important to have another mAb treatment option that binds to a different antigen site than currently approved mAbs for preterm infants and those with underlying medical conditions, as well as those infants who have no predisposition to severe RSV disease. The substantial global burden of hospitalizations and childhood deaths due to RSV necessitates the importance of additional RSV therapies for the prevention of RSV.

2.2. About the product

Clesrovimab is a fully human immunoglobulin G1 kappa (IgG1κ) neutralising monoclonal antibody with a triple amino acid substitution (YTE) in the Fc region which increases binding to the neonatal Fc receptor leading to an extended serum half-life. Clesrovimab provides passive immunity by targeting the RSV outer membrane fusion (F) protein to prevent viral entry into cells.

Clesrovimab binds to a conserved epitope on antigenic site IV on the fusion F protein. Clesrovimab binds to RSV pre-fusion F glycoprotein and post-fusion F glycoprotein with equilibrium dissociation constant values (KD) of 71 pM and 480 pM, respectively.

The product has not yet been approved in any market.

The proposed indication is the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

The proposed posology dose is 105 mg administered as a single 0.7 mL single intramuscular (IM) injection. For neonates and infants born during the RSV season, clesrovimab should be administered starting from birth. For infants born outside the RSV season, it should be administered once prior to the start of their first RSV season.

2.3. Type of Application and aspects on development

The clinical program included 4 clinical studies in infants to support the proposed indication of prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV:

• Two ongoing global pivotal studies supporting efficacy, safety, and PK of clesrovimab, including SNA and ADA assessments, in the following populations:

- MK-1654-004: Phase 2b/3 study in healthy preterm (gestational age ≥29 weeks to <35 weeks) and full-term infants (gestational age ≥35 weeks)

- MK-1654-007: Phase 3 study in infants at increased risk for severe RSV disease due to risk factors of CHD, CLD, or prematurity (born at ≤35 weeks gestational age)

• Two completed early phase studies supporting the safety of clesrovimab, both of which enrolled the same infant population as MK-1654-004 and evaluated a comparable dose of clesrovimab:

- MK-1654-002: Phase 1b/2a study in infants in Panels D and E dosed with 100 mg of clesrovimab

- MK-1654-008: Phase 1 study in infants in Panel C dosed with 105 mg of clesrovimab

Clinical development in infants:

Study MK-1654-004 is an ongoing Phase 2b/3 double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of clesrovimab for the prevention of RSV-associated MALRI in in healthy preterm (gestational age ≥29 weeks to <35 weeks) and full-term infants (gestational age ≥35 weeks) and entering their first RSV season. In this study, 3632 participants were randomized (2421 in the MK-1654 group, 1211 in the placebo group) out of which 2412 and 1202 received study intervention (single IM dose of clesrovimab (105 mg) or placebo, respectively). The primary efficacy hypothesis was evaluated by calculating the efficacy of clesrovimab compared to placebo with respect to the endpoint of RSV-MALRI Days 1 through 150 postdose. This study is considered as the main, pivotal body of evidence for the current application.

Study MK-1654-007 is an ongoing Phase 3 partially blinded, randomized, active-controlled study to evaluate the safety, tolerability, and efficacy of MK-1654 versus palivizumab and the PK of MK-1654 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. In this study, up to date 901 participants were randomized (450 in the MK-1654 group, 451 in the palivizumab group), out of which 446 received Dose 1 of study intervention (single IM dose of clesrovimab 105 mg). Since the study population comprises infants at increased risk of severe RSV disease, this study is considered also as pivotal evidence as well as the main study. Notably, the efficacy of clesrovimab in healthy infants is extrapolated to infants at increased risk for severe RSV disease, based on the comparable PK exposure with healthy infants in Study MK-1654-004. The primary objective was safety and efficacy outcomes were included as secondary objectives.

MK-1654-002 was a Phase 1b/2a, randomized, placebo-controlled, single ascending dose, multisite, global, double-blind study to evaluate the safety, tolerability, and pharmacokinetics (PK) study of MK-1654 in 181 healthy preterm and full-term infants. Preterm infants were randomized in a dose escalation paradigm by panel to Panels A, B, C and D, and full-term infants were randomized to Panel E only. Available safety, tolerability, and PK data from Panels A, B, and C were analyzed to inform the final dose level and allocation of participants in Panel D for preterm infants and Panel E for full-term infants. Furthermore, clesrovimab efficacy in infants was also evaluated as an exploratory objective. In this study, 183 participants were randomized and 181 were dosed and included in the analysis of safety.

MK-1654-008 was an open-label and multi-site study to evaluate safety and tolerability of MK-1654 in 75 participants. Healthy Chinese male adults (aged ≥18 to ≤55 years), children (aged ≥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 (14 days) to ≤1 year (365 days)) were sequentially enrolled into Panels A, B and C, respectively.

Clinical development in adults:

The early development program also included studies in healthy adults (MK-1654-001, MK-1654-003, and MK-1654-008 Panel A) to evaluate PK and safety of clesrovimab prior to proceeding into infants. The CSRs for these studies were provided in this initial marketing application but are considered less relevant for this MAA.

2.4. Quality aspects

2.4.1. Introduction

Enflonsia finished product (FP) is presented as solution for injection containing 105 mg of clesrovimab as active substance (AS).

Other ingredients are: histidine, histidine hydrochloride monohydrate, arginine hydrochloride, sucrose, polysorbate 80 and water for injections.

Enflonsia is supplied in a pre-filled syringe (Type I glass) with a plunger stopper and a tip cap with or without needles. Enflonsia is available as the following pack sizes:

- 1 pre-filled syringe
- 1 pre-filled syringe + 1 needle
- 1 pre-filled syringe + 2 needles
- 10 pre-filled syringes

- 10 pre-filled syringes + 10 needles
- 10 pre-filled syringes + 20 needles
- Multipacks containing 50 (5 packs of 10) pre-filled syringes

2.4.2. Active Substance

2.4.2.1. General information

The active substance is clesrovimab (company code: MK-1654), is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. It is composed of two identical heavy (Igγ1) and two identical light (Igκ) chains linked by inter-chain disulfide bonds, it contains 32 cysteine residues.

The correctly folded antibody molecule includes 4 interchain (two in the hinge region and two connecting the heavy chain (HC) and light chain (LC)) and 12 intrachain bonds (four in each HC and two in each LC). Three-point substitutions were introduced into the Fc region of the parental mAb (RB-1) to extend the half-life of clesrovimab.

The amino acid sequence of the HC and LC contain 457 and 214 amino acids, respectively. The C-terminal Lys 457 is mostly cleaved off. There is one glycosylation site in the heavy chain (Asn 307). The molecular mass of the most abundant form, with C-terminal truncation of Lys 457 and N-linked glycosylation at Asn 307 by G0F oligosaccharides is 149,407 Da.

Clesrovimab binds to a highly conserved epitope of the respiratory syncytial virus (RSV) fusion (F) protein, neutralizing the virus by preventing virus/host cell fusion. The substitutions in the Fc region result in improved affinity to neonatal Fc receptor (FcRn) and extended antibody half-life *in vivo*. Fc-related effector functions are not required for clesrovimab mechanism of action (MoA).

2.4.2.2. Manufacture, characterisation and process controls

Manufacturers

The active substance is manufactured at Lonza Biologics, Inc. (101 International Drive Portsmouth, NH 03801, USA). The name, address and responsibility of all active substance manufacturers involved in the manufacturing, quality control and stability testing, as well as storage and testing of the master cell bank (MCB) and working cell bank (WCB) have been provided.

All active substance manufacturing sites are GMP compliant.

Description of manufacturing process and process control

The active substance is expressed in a CHO cell line and produced in a fed-batch process.

The fed-batch process involves bolus additions of concentrated nutrient feeds. When the harvest criteria have been reached, the content of the bioreactor is harvested by centrifugation. The harvested cell culture fluid (HCCF) is further processed through protein A chromatography, viral inactivation and depth filtration (VI/DF), anion-exchange chromatography (AEX) and cation-exchange chromatography (CEX).

After chromatographic purification, a viral filtration (VF) unit operation is used, and the ultrafiltration diafiltration (UF/DF) unit operation concentrates and exchanges the product into the diafiltration

buffer. The UF/DF product (UFP) is filtered and then diluted with formulation and dilution buffers to achieve the final formulation.

The formulated product is filtered, dispensed into AS storage bags, frozen, and stored. During filling of AS in the storage bags, samples are collected in scale-down bags and submitted for release and stability testing.

One AS batch is derived from a single WCB vial. Unique lot numbers are assigned to each individual AS batch. The manufacturing steps have been properly described. Flow diagrams have been provided for both upstream and downstream processing.

Process parameters with their criticality classification and acceptable ranges, and in-process controls (IPC) with respective acceptance criteria have been listed for each step. In-process controls to ensure product safety (e.g. bioburden, viral testing) have been properly defined.

Control of materials

Raw materials, culture media, and buffer components used during manufacturing of the active substance are listed together with their intended use, acceptance criteria and compliance with Ph. Eur., USP and NF. All raw materials are free from any source of human and animal components.

For the generation of the gene construct, RSV fusion glycoprotein-specific B cells were isolated from human memory B cells, cultured and screened for RSV binding and neutralization activity. RNA from the selected clone was used for molecular cloning. The construction of the expression vector is described in sufficient detail.

An animal-derived raw material was used in the initial stages of cell line development, and the related TSE-Certificate of Suitability has been provided.

A two-tiered cell banking system consisting of Master Cell Bank and Working Cell banks has been established. For commercial manufacturing purpose, a limit of *in vitro* cell age (LIVCA) has been established and cells collected from the production bioreactor on the day of harvest and used to generate the end of production cell bank (EOPCB) and a post-production cell bank (PPCB). Characterisation of the cell banks includes testing of post-freeze thaw viability and cell growth, cellular morphology and growth characteristics, identity (Chinese hamster) and purity (sterility, mycoplasma, *in vitro/in-vivo* adventitious viruses, viruses, retroviruses). The genetic stability of the expression construct at the LIVCA was confirmed in cells from the MCB, WCB, and PPCB by southern blotting, northern blotting, gene copy number, and sequence verification.

Storage stability of the cell banks is assessed by viability and relevant growth or metabolic characteristics when vials are thawed for propagation (the WCB vial thawed for production) and MCB thawed for producing new WCB vials), as described by ICH Q5D. If a vial is not thawed within a specified period a test thaw will be performed. The strategy for preparation, characterisation, qualification, and release of a new WCB is satisfactory.

The information provided is adequate and sufficient.

Control of critical steps and intermediates

The control strategy presented includes classification of process parameters as critical process parameters (CPPs) based on an impact to critical quality attributes (CQAs) and identification of process parameters (PP) impacting process consistency, establishment of in-process controls (IPC) and in-process attribute limits and finally establishment of proven acceptable ranges (PAR).

Furthermore, the selected process parameters were evaluated in PC (process characterisation) studies via design of experiment (DoE) and/or One-Factor-at-a-Time (OFAT) studies. For each unit operation,

the process parameter assessment ranges were set based on the feasible process parameter ranges during manufacturing, which considered the anticipated normal operating ranges (NOR), equipment and manufacturing tolerances, clinical manufacturing experience, available development experience, and prior knowledge from similar commercial manufacturing processes and sites.

According to the guideline ICH Q8 and ICH Q11, the control strategy should be developed by establishing the quality target product profile (QTPP) and identification of CQAs, based on a risk assessment, early development studies and characterisation studies. The QTPP and the rationale behind the designation of properties or characteristics as CQA have been provided and sufficiently discussed in the finished product pharmaceutical development.

Process validation

Process validation studies were performed to demonstrate that the active substance manufacturing process operates within the pre-defined Process Performance Qualification (PPQ) acceptance criteria and is able to ensure manufacturing of active substance of defined quality.

Several consecutive PPQ batches, at full commercial scale, were tested. The PPQ studies were designed to evaluate process consistency through verification that the CPPs and PPs remained within their respective acceptable ranges during the manufacturing process. CQAs, IPCs, and monitored attributes were also assessed during the PPQ campaign. The PPQ results demonstrate that the batches met the pre-defined acceptance criteria.

Impurities clearance studies were performed in small-scale models to confirm the ability to remove impurities from the process stream. Robustness of the clearance of process-related impurities has been confirmed for post-viral inactivation depth filtration and chromatography products.

Bioburden and endotoxin control studies were executed for the PPQ campaign to examine the potential for microbial ingress into the process stream from the manufacturing environment and the potential for microbial proliferation due to processing conditions if microbial ingress has occurred. All bioburden and endotoxin control study results passed the PPQ acceptance criteria.

The AS manufacturing process does not have any isolated intermediates that are released via testing prior to the continuation of the manufacturing process. There are several intermediates that can be held for defined periods of time and temperature ranges. In order to set appropriate storage conditions for each process intermediate, biochemical stability was assessed by extended hold studies of samples, collected during manufacture of PPQ batches, and stored in small-scale containers that are representative of the large-scale containers. Small-scale samples of each intermediate were aliquoted from different commercial scale batches and stored in representative containers at room temperature and refrigerated. Samples for each timepoint were frozen until analytical testing. The shortest hold time duration validated was set as the biochemical hold time for the intermediate.

Lifetime studies of Protein A, anion exchange (AEX), and cation exchange (CEX) chromatography resins were performed using small-scale models.

Shipping has been properly validated.

Single-use parts used in the clesrovimab AS manufacturing process (Bio Process Containers (BPCs), tubing, aseptic connectors, filters, membranes, depth filters, and other miscellaneous disposable items) were classified as having a high, medium, or low potential risk for contributing leachables into the clesrovimab AS during routine manufacture. A leachable simulation study was conducted for the AS filled into representative small-scale bags, and it is concluded that there is no risk for patient safety. A certificate of release and representativeness of the small-scale bags used for leachable simulation study have been provided.

Conditions and circumstances at which reprocessing is allowed are listed. Small-scale validation studies have been performed which confirmed that those reprocessing steps can be performed with no impact on product quality.

Manufacturing Process Development

The active substance manufacturing process was developed through two processes (Process 1 and Process 2) and involved three sites.

Process 1 was employed to produce preclinical toxicology, *in vitro* tissue cross-reactivity, reference material, and early phase clinical trial materials. Process 2 was employed to produce late phase clinical trial materials and prepare the Primary Reference Standard.

Process 2 at the commercial site is a scale up Process 2 from the clinical site employed to produce Primary Stability, Process Performance Qualification (PPQ), Secondary Reference Standard and commercial batches. Clinical FP batches used in Phase 2b/3 and later clinical studies have been manufactured under GMP with Process 2.

Development of the manufacturing process is properly described. The rationale behind the changes has been provided.

A detailed process comparison has been provided. Analytical comparability of active substance manufactured with the Process 1 and Process 2 has been accurately investigated by comparison of release and stability results, extended characterisation and forced degradation. Analytical comparability has been confirmed.

The active substance manufacturing Process 2 was transferred from the clinical facility to the commercial facility. Minor process changes were made for facility fit to improve manufacturing efficiency and decrease process variability. Process comparability takes into consideration the risk associated with the changes, the CQA/IPC/Process Monitored Attributes eventually impacted by the change, and the impact on stability, but no high-risk changes were identified. A range of experience (RoE) approach for the assessment of process performance. Comparability of the upstream steps focused on cell viability and antibody titer and step yield. Comparability of the downstream steps focused on Purification Unit Operations and attributes N-linked glycosylation, high molecular weight species, fragmentation, charge variants, process residuals. Comparability of the AS manufacturing Process 2 has been demonstrated.

Analytical comparability has been accurately investigated by comparison of release and stability results, extended characterisation and forced degradation. Analytical comparability of AS has been confirmed. Individual results of the batches are provided and all differences (including the polysorbate 80 levels) are sufficiently justified. Individual results of comparative forced degradation study are provided.

Process characterisation studies were performed with small-scale models representative of the commercial manufacturing scale process. Qualification of the small-scale models used for PC is provided for all unit operations. Results confirm that the small-scale models are properly qualified and representative of the commercial manufacturing scale process.

Characterisation

Characterisation of the active substance has been addressed according to the Guideline on development, production, characterisation and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008 and general Ph. Eur. monograph 0784.

A broad range of methods was applied to analyse physicochemical and immunochemical properties, biological activity, purity and impurities. Results provided in this section only refers to one batch, but

results from additional batches, including batches from all different manufacturing processes, have been provided in Section 3.2.S.6 Analytical comparability.

Results of the characterisation and development testing indicate that the AS exhibits properties representative of a fully human monoclonal antibody containing heavy and light chains bound by disulfide linkages with typical levels of heterogeneity in its mass, glycosylation, and charge profiles, and comparable results were obtained for most of the testing. Biological characterization of clesrovimab indicates that this antibody has the ability to bind RSV-F with high affinity. Binding activity of the Fab domain has been confirmed. A cell-based RSV neutralization assay confirms the ability of clesrovimab to preventing entry of a RSV reporter virus.

Product- and process- related impurities and potential contaminants are adequately discussed. HMW species increase over time on stability but no impact potency has been observed. Structural characterisation results of the charge variants, which focused on the analyses of the size and fragmentation profile, show that the majority of the AS on main peak contains IgG with consensus sequence and predicted glycoform.

The majority of the acidic variants were found to have similar post-translational modifications as main peak.

The nitrosamine risk assessment provided confirms that there is no identified risk of nitrosamine impurities in the AS process or the associated primary packaging components.

Absence of contamination form mycoplasma and adventitious virus is adequately guaranteed by the measures established to inactivation and/or remove adventitious viruses. Process controls are also employed to minimize the risk of microbial contamination. The information provided is sufficient.

2.4.2.3. Specification

Active substance specification for clesrovimab, including methods to evaluate appearance, clarity, colour, identity, potency, protein concentration, purity/impurities, sterility, bacterial endotoxins, is presented.

The release specification includes general compendial tests (appearance, clarity and degree of opalescence, colour and pH), microbiological compendial tests as bioburden and bacterial endotoxins, and in-house established tests for identity, protein concentration, polysorbate 80, purity/impurities.

Potency is determined by a functional cell-based assay reflecting the proposed mechanism of action (MoA) of clesrovimab.

The shelf-life specification differs from the release specification for absence of identity and process related impurities, which is acceptable since they are not product stability indicating parameter.

Acceptance criteria have been established. The proposed acceptance criteria for compendial tests (appearance, clarity and degree of opalescence, colour and pH, bioburden and bacterial endotoxins) are considered adequately justified. AS and FP specifications have been tightened for some parameters to reflect the reported release and stability data. The proposed specification for protein concentration was maintained. AS release/stability specification for potency has been tightened. In conclusion, the proposed active substance specifications are acceptable.

<u>Analytical methods</u>

The analytical methods are properly described. Equipment, reagents, test procedure (solution and sample preparation, chromatographic conditions), typical chromatograms/ electropherograms, system suitability criteria, sample acceptance criteria, and data processing are in most of the cases provided.

Unequivocal names for in-house analytical methods are provided in the specification table, method description and method validation summaries.

Validation reports are provided for all analytical methods. Methods for identification, potency, protein concentration, charge variants, purity and polysorbate 80 concentration have been validated.

Since AS and FP have identical sample matrices, the methods validation has been done only with AS, which is acceptable. Methods have been properly validated.

Batch analysis

Batch analysis results are provided for several batches, including representative development, clinical, stability, PPQ and commercial active substance batches. All batches were released according to the specifications applicable at the time of release and all results were generated using test methods in place at the time of testing. Method versioning and evaluation of the impact of method changes over time is presented.

All results provided comply with the proposed specifications, therefore it has been demonstrated that active substance of consistent quality is manufactured by the proposed manufacturing process.

Reference standards

The history of the reference standards used during development of clesrovimab is properly described. The primary reference standard (PRS) is used for qualification and re-evaluation of secondary reference standard (SRS) and of a new PRS. The SRS is used for clesrovimab AS and FP routine release, stability, in-process and extended characterisation testing. The acceptance criteria for standard qualification are the same as the AS release specifications valid at the time of qualification, except for the potency and protein concentration. The strategy to avoid potential drift is explained in detail.

Container closure

The active substance is filled into sterile single-use containers. A schematic drawing and a certificate of release are provided. The storage bags comply with related USP and Ph. Eur. 3.1.7. Suitability of the container closure is demonstrated by container-closure integrity testing (performed on AS storage bags containing AS after shipping, thawing, and emptying bags) and results of the stability of AS in the container-closure system in small-scale bags. Suitability of the contact material by leachables and extractables studies and physical protection of the AS from the external conditions and handling anticipated during transportation have been confirmed.

2.4.2.4. Stability

Stability studies have been performed in line with relevant ICH guidelines with three primary stability batches manufactured using a process representative of the commercial scale (Process 2) and with commercial site GMP stability and PPQ batches (Process 2). Supportive stability studies were performed in support of clinical studies with development and early clinical batches.

Primary stability data are provided for additional temperatures. Stability studies for PPQ batches have been started at long-term storage conditions.

Since comparability between primary batches (Process 2) and PPQ batches (Process 2) to PPQ batches has been fully confirmed, results of the primary stability studies can be taken to support the shelf-life claim. Data from the freeze/thaw study supports the time out of storage (TOS) claim.

Based on the review of the stability data, the claimed shelf-life for the active substance when stored at the recommended conditions is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Enflonsia 150 mg/mL (105 mg/PFS in 0.7 mL) is a sterile, single use, preservative-free, colourless to slightly yellowish solution for injection containing 105 mg of Clesrovimab as active substance. Other ingredients are: histidine, histidine hydrochloride monohydrate, arginine hydrochloride, sucrose, polysorbate 80 and water for injections.

Enflonsia is supplied in a pre-filled syringe (Type I glass) with a plunger stopper and a tip cap with or without needles.

The qualitative and quantitative composition of Enflonsia has been presented. The finished product is formulated with compendial excipients which are compliant with appropriate Ph. Eur. Monographs. There are no novel excipients. No excipients of human or animal origin are used in the manufacture of the FP.

Formulation development

The Applicant has based their formulation development on a Quality Target Product Profile (QTPP) considering dosage form (sterile liquid 150 mg/mL), commercial image (0.7 mL liquid dose in 1.5 mL PFS), dose/administration, and stability profile (minimum 2 years at 2-8°C). The sterile FP has the same formulation as the AS.

Design of Experiments (DOE) studies with a range of excipient concentrations around target levels were performed to assess the stability of clesrovimab formulation in comparison to formulations composed of high and low concentrations of excipients.

Manufacturing process development

Adequate details of manufacturing process development steps have been provided such as thawing, FP formulation, bioburden reduction and sterile filtration, filling and stoppering. In addition, material compatibility and photostability have been evaluated.

During development two different AS processes (Process 1 and Process 2) differing in protein and excipient concentrations (see above) have been used to manufacture FP. Three different sites have been used during FP manufacturing development.

A comparative assessment between FP from both AS processes has been provided. Evaluation criteria for comparison of batch release data are the range of experience (RoE) for clesrovimab Process 1. Analytical comparability was evaluated considering release test results, extended characterization analyses, and stability profiles. Provided results show highly comparable data/chromatograms/electropherograms for most tests. It is agreed, that clesrovimab finished product manufactured with clesrovimab Process 1 and Process 2 finished products are comparable.

A comparison of FP manufacturing sites has been provided describing performed changes or site related differences in the manufacturing process.

A separate analytical comparability evaluation has been presented of FP manufacturing at the clinical site (vial presentation) and the intended commercial FP site (PFS presentation). Comparability was evaluated considering release test results, extended characterization analyses, and stability profiles.

Differences are minor and are justified by the limited number of manufactured vial batches and the analytical variabilities of methods applied. All PFS batches analysed met release specifications and no concern is raised. It is agreed, that clesrovimab finished product manufactured in vial and PFS presentations are comparable.

Product Quality Risk Assessment and Integrated Control Strategy

Using the Product Quality Risk Assessment an Integrated Control Strategy was developed. An overall risk level was determined for each PQA considering severity, likelihood of occurrence and detection. The integrated control strategy comprises the following elements: procedural control, raw material control, characterisation, periodic testing, routine monitoring, in-process control, and AS/FP specifications.

The development of the control strategy is well described, and the assigned severity scores are appropriately justified. The summarised integrated control strategy for each critical QA is considered suitable to consistently control for a safe and effective product.

Extractable and leachable studies have been performed to evaluate the compatibility of the syringe with the finished product. In summary, the proposed container closure system appears suitable for Enflonsia.

2.4.3.2. Manufacture of the product and process controls

The name, address and responsibility of all finished product manufacturers involved in the manufacturing, quality control and stability testing, assembly and packaging, batch release have been provided.

The batch release site for the EEA (European Economic Area) is Merck Sharp and Dohme B.V., Waarderweg 39 Haarlem, 2031 BN, Netherlands.

All sites involved in the manufacturing process of the finished product are GMP compliant.

The manufacturing process of the FP includes, thawing of AS, formulation, bioburden reduction filtration and sterile filtration. The bulk FP solution is filled into the final containers, addition of stoppers followed by visual inspection finishes the manufacturing process. The final assembly process includes assembly of plunger rod, addition of a product label, and backstop placement. The flow diagram of the manufacturing of the finished product is provided.

Minimum and maximum batch sizes are sufficiently supported by process validation data.

The provided information on the finished product manufacturing process is considered adequate. Process parameters and in-process controls together with their acceptable ranges are listed, reflecting results from manufacturing process development activities and from process validations. Information on processing limits and hold time limits have been provided for processing steps thaw time, FP formulation time and sterile filtration time; the maximum processing times have been investigated during process validation. Automatic generation of batch numbers is briefly described.

Process Validation

Validation of the finished product manufacturing process at the commercial manufacturing site included three commercial scale MK-1654 batches. In total, three different AS batches were used for FP process validation in varying combinations. It is agreed that AS variability is sufficiently covered within the three FP PPQ batches. Batch sizes reflecting commercial scale, were considered in the process validation studies. Critical steps identified during product development activities have been addressed

during process validation and results were compared to pre-defined validation criteria. Furthermore, release test results of the validation batches have been cross-referenced to dossier section 3.2.P.5.4. Release test results for the three PPQ batches complied with acceptance criteria and indicate a consistent manufacturing process. All in-process controls and CQAs met pre-defined criteria.

Microbial and sterile filtration of the bulk finished product was validated by a microbial retention study and bubble point testing. Presented data demonstrate that sterile filtration can be considered as successfully validated.

The procedures for media fills are described in order to provide information on the reliability and reproducibility of the aseptic process. Respective successful initial qualification results have been provided. In addition, a single process simulation was performed using clesrovimab manufacture specific components. Process simulations can be considered successful. Periodic process simulation validations (media fills) for the PFS line are performed.

Transport of Enflonsia bulk filled syringes and final product is well described and has been validated by several studies. Transport of Enflonsia bulk filled syringes and final product is considered validated.

The final assembly PPQ met all predetermined acceptance criteria and it is agreed that the assembly process is validated to consistently meet predetermined quality attributes.

2.4.3.3. Product specification

The proposed finished product release and shelf life specifications have been presented and comply with the requirements of general monographs *Ph. Eur.* 2031 (Monoclonal Antibodies for human use) and 0520 (Parenteral Preparations) as well as guideline ICH Q6B. Finished product specification includes testing for appearance and visible particles, clarity, colour, identity, potency, protein concentration, purity/impurities, sterility, and bacterial endotoxins.

The specifications were set in line with current EMA Guidelines and Ph. Eur. requirements and respective acceptance criteria are appropriately justified. Several batches manufactured using Process 2 have been used for justifications of commercial release and shelf-life specifications. Only FP related tests have been addressed under dossier section 3.2.P.5.6 Justification of Specifications. Tests used for AS and FP specifications are discussed under dossier section 3.2.S.4.5.

Acceptance criteria defined for FP related tests are considered sufficiently justified. For attributes tested at AS and FP level, please refer to section 3.4.5. of this report.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. It can be concluded that it is not necessary to include any elemental impurity controls. A risk assessment regarding the potential presence of nitrosamines was provided based on the principles in ICH M7. The nitrosamine risk assessment provided concluded that the risks of nitrosamine presence is negligible and therefore there is no identified risk of nitrosamine impurities.

Analytical procedures

The analytical methods appear adequate for their intended purpose. Finished product specific test items are controlled by compendial methods. Container closure integrity is tested, and syringe functionality is tested.

Description of FP related non-compendial methods (container closure integrity and syringe functionality) has been presented. Methods used for control of active substance as well as control of finished product are described and discussed in dossier sections 3.2.S.4.2 and 3.2.S.4.3.

The presented validation and verifications of the analytical methods specific for FP are adequate and in accordance with ICH Q2(R1) and demonstrate the suitability of the analytical procedures for their intended use.

Batch analyses

Batch analyses data have been presented for representative development, clinical, stability, process performance qualification (PPQ), and commercial clesrovimab finished product batches. In detail, batch analysis data for PFS presentation has been presented for several PPQ batches and commercial batches from the same site and using the same Process 2. Furthermore, several primary stability batches and additional development batch from the commercial manufacturing site using Process 2 have been presented. In addition, one batch employing Process 2 has been presented from a research manufacturing site. Clinical batches originated from two sites utilizing Process 2 and Process 1.

All batches complied with the pre-defined acceptance criteria valid at the time of release using test methods in place at time of testing

Reference standards or materials

Please refer to active substance section "Reference Standards or Materials".

Container Closure System

The container closure system for the finished product is a pre-filled syringe (PFS) integral drug-device combination consisting of a 1.5 mL type I glass barrel with luer-lock adaptor, a rigid tip cap and a plunger stopper. Syringe barrel and tip cap are siliconized with medical grade silicone. CE-marked needles are packaged with the syringes. A declaration of conformity and a copy of the CE certificate have been provided for the needle.

According to the Article 117 of the Medicinal Device Regulation (EU) 2017/745 (MDR), a CE certificate or Notified body opinion on the conformity of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR should be provided. A Notified Body Opinion report from July 2024 has been presented and the objectives of this assessment were found to have been met.

Information has been provided for the sterilisation of the primary container closure. The sterilisation process of the syringe has been validated according to Ph. Eur. 5.1.1. and 5.1.2. and the control of the residue from the sterilisation process have been demonstrated.

Extractable and leachable studies have been performed to evaluate the compatibility of the syringe with the finished product. In summary, the proposed container closure system appears suitable for Enflonsia.

2.4.3.4. Stability of the product

A shelf life of 30 months when stored at 2 °C – 8 °C is claimed for the finished product.

The stability data provided included 30 months data from three GMP batches and three PPQ batches. All batches have been manufactured using Process 2 at the intended commercial manufacturing site. In addition, stability data from accelerated and stress studies have been provided for those batches.

Based on a comparability study the GMP batches can be considered as being representative of the PPQ/commercial batches. As such and in accordance with ICH Q5C and Q1A(R2) these batches could be used as primary stability batches in order to support the shelf life of 30 months at 2 °C – 8 °C.

At the intended storage condition of 5°C, all test results complied with the shelf-life specifications for the three primary stability batches. Potency results were relatively stable over time.

At the accelerated conditions presented, stability data are comparable. At stress storage conditions, a similar but more pronounced stability behaviour was shown for tested batches for up to three months.

For one batch stability of the integral drug-device combination has been shown. Tested attributes conformed with acceptance criteria.

Available 12 months stability data for PPQ batches show a similar stability behaviour at the intended storage condition of 5°C, at accelerated, and at stress storage conditions.

Supportive stability data have been presented for batches originating from all manufacturing sites, using manufacturing processes 1 and 2 in vial and PFS presentation. Results support conclusions from discussed PPQ and Primary Stability batches.

Results from ICH photostability study conducted according to ICH Q1B indicate influence of light conditions. Therefore, the product should be stored in the secondary package to maintain protection from light.

Results from cold stress study show, that temperature excursions can be supported.

In conclusion and based on the review of the stability data a shelf life of 30 months for the finished product when stored at 2 °C – 8 °C is considered acceptable. Enflonsia may be kept at room temperature (20 °C - 25 °C) for a maximum 48 hours. After removal from the refrigerator, it must be used within 48 hours or discarded.

2.4.3.5. Adventitious agents

The strategy presented to ensure adventitious agents safety of Enflonsia with respect to both non-viral and viral adventitious agents is considered satisfactory.

Endogenous and adventitious viruses can be cleared by the downstream manufacturing process, which includes chromatography steps and a dedicated viral filtration.

The clesrovimab AS manufacturing process uses a CHO cell line which is known to produce non-infectious type C retrovirus-like particles. The ability of the process to clear such particles was assessed. Accordingly, a panel of model viruses was chosen for use in viral clearance (VC) studies in qualified scale-down models to demonstrate the ability of the downstream process to clear retrovirus, as well as to clear viruses in general.

A summary of the viral clearance study results obtained under set-point conditions is provided. The results from the calculated cumulative the $\log_{10}$ reduction value (LRV), are expressed as the sum of the individual step LRVs of the purification process.

Overall, the downstream manufacturing process for clesrovimab includes effective viral clearance steps and supportive steps. A safety assessment for retrovirus was determined to be consistent with ICH Q5A Guidance.

The risk of contamination of adventitious agents appears adequately controlled. Parameters considered to have impact to viral clearance claims were considered during establishment of the overall control strategy.

A TSE-Certificate of Suitability has been provided for an animal derived raw material used during the development phase confirming that it conforms to the requirements as defined in the Guideline

EMEA/410/01 "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

In conclusion, the information provided is sufficient and acceptable and demonstrate that adventitious agents safety including TSE have been sufficiently assured.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

Clesrovimab is a fully human IgG1 mAb developed to protect infants from RSV infection. Three substitutions were introduced into the Fc region of the parental mAb RB-1 to extend the half-life, by reducing clearance, thereby allowing protection with a single administration.

Clesrovimab (MK-1654) is manufactured through a typical manufacturing process for mAbs. The active substance is expressed in CHO cells and manufactured with a scale fed-batch process. The process includes purification though protein A chromatography, viral inactivation and depth filtration, anion-exchange chromatography, cation-exchange chromatography, viral filtration and ultrafiltration diafiltration. The manufacturing process is properly described. Manufactures are listed. An updated QP declaration has been provided. All active substance manufacturing sites are GMP compliant.

Raw materials, culture media, and buffer components, used during AS manufacturing are listed with their quality standard and intended use. Excipients in the final formulation comply with Ph. Eur. requirements. Composition of upstream media and feeds and of downstream buffers and solutions is provided. All raw materials used are free from any source of human and animal components.

The expression system and the generation/selection of a stable-transfected production cell line are properly described. The cell banks are properly described, characterised, and qualified in accordance with ICH guidelines.

The control strategy to ensure consistent manufacture of the AS is based on the control of all critical unit operations of the manufacturing process. CPPs were identified based on their impact on CQAs, PPs impacting process consistency and determined proven acceptable ranges for all CPPs and PPs impacting consistency. A process characterisation risk assessment was performed to identify parameters to be included in the process characterisation studies. Qualification of the small-scale models used for process characterisation has also been provided.

Process performance validation with several PPQ batches confirmed manufacturing of AS of consistent quality meeting all pre-defined specifications and quality attributes. Most of the deviations have been fully assessed and confirmed to not impact the validity of the PPQ campaign. There are no intermediates requiring long term storage, and intermediate hold times were properly validated. Reprocessing of the viral reduction filtration or final filtration was properly validated. Re-use of process chromatography resins across batches is supported by validation studies on small scale models. Re-use of ultrafiltration/diafiltration (UF/DF) membranes was confirmed at production scale. Validation of the clearance of impurities was done with small-scale model. Robustness of clearance of process-related impurities was confirmed. Absence of potential microbial ingress and proliferation was confirmed by bioburden and endotoxin tests.

The AS manufacturing process was developed through two processes (Process 1 and Process 2) and involved three sites. Clinical FP batches used in Phase 2b/3 and later clinical studies have been manufactured under GMP with Process 2 and commercial batches are manufactured with Process 2. Development of the manufacturing process, including process changes after the PPQ campaign, is properly described. The rationale behind the identification of CQAs is provided. Comparability between

Process 1 and Process 2 has been confirmed. Analytical comparability of AS from Process 1 and Process 2 has been accurately demonstrated by comparison of release and stability results, extended characterisation and forced degradation, and analytical comparability has been confirmed. Comparability between Process 2 at the clinical site and Process 2 at the commercial site has been demonstrated. Analytical comparability of AS from Process 2 at the clinical site and Process 2 at the commercial site has been properly addressed by comparison of release and stability results, extended characterisation and forced degradation, and sufficiently demonstrated.

The active substance has been properly characterised. Removal of product- and process- related impurities and potential contaminants has been demonstrated. The nitrosamine risk assessment report provided covers all manufacturing process steps.

The acceptance criteria for the specifications are agreed**.** AS release/stability specification for potency has been tightened. AS and FP specifications have been tightened to reflect the reported release and stability data. Analytical methods are properly described. Validation reports are provided. All methods are properly validated.

Development of the reference standard is properly described. The primary reference standard (PRS) is used for qualification and re-evaluation of SRS and of a new PRS, and a secondary reference standard (SRS) is used for clesrovimab AS and FP routine release, stability, in-process and extended characterisation testing.

AS is stored in sterile single-use bags. Specifications of the active substance container closure are provided. A container-closure integrity study was performed for AS in bags after shipping, thawing, and emptying bags. Stability of AS in the container-closure system, suitability of the contact material by leachables and extractables studies and physical protection from external conditions and handling during transportation were confirmed in small-scale bags.

Based on the stability data provided, the claimed self-life for the active substance at the recommended storage conditions, is acceptable.

Finished product

Clesrovimab finished product 150 mg/mL (105 mg in 0.7 mL) solution for injection, liquid in pre-filled syringe (company´s name: MK-1654) is a sterile, single use, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution for injection containing Clesrovimab as active substance. Other ingredients are histidine and histidine hydrochloride monohydrate as buffer, arginine hydrochloride as stabilizer, sucrose as tonicity agent, polysorbate 80 as surfactant and water for injections as solvent.

The container closure system for the finished product is a pre-filled syringe (PFS) integral drug-device combination consisting of a 1.5 mL type I glass barrel with luer-lock adaptor, a rigid tip cap and a plunger stopper. The excipients comply with the requirements of the respective Ph. Eur. monographs and no novel excipient is used in the FP. No excipients of human or animal origin are used in the manufacture of the FP.

The FP is produced by a standard manufacturing process before storage at 2-8°C. The manufacturing process development has principally been described in sufficient detail. The definition of CQAs and overall control of the process appears reasonable. Process characterisation, process validation and batch data indicate that the manufacturing process reliably generates finished product meeting its predetermined specifications and quality attributes.

The performed process validation followed a traditional approach on three consecutive, commercial scale batches. The information on process validation contains the most important elements in order to demonstrate validity of the manufacturing process.

Analytical FP data was compared from manufacturing Process 1 and Process 2 derived from three different sites. Analytical comparability was successfully shown considering release test results, extended characterisation analyses, and stability profiles.

In a second comparability study, FP from clinical manufacturing site was compared to material produced at the intended commercial manufacturing site. Comparability was evaluated considering release test results, extended characterisation analyses, and stability profiles. It is agreed, that clesrovimab finished product manufactured in vial and PFS presentations is sufficiently demonstrated.

Reference standards are described under the active substance section.

A shelf-life of 30 months is proposed for the finished product when stored at 5°C in the commercial container closure system, protected from light. This is endorsed.

Overall, the manufacturing process is found to be well controlled and to be able to consistently produce finished product of acceptable quality.

The strategy presented to guarantee safety of Enflonsia with respect to both non-viral and viral adventitious agents is considered satisfactory. Parameters considered to have impact to viral clearance claims were considered during establishment of the overall control strategy. The risk of contamination of adventitious agents appears adequately controlled.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Enflonsia is considered acceptable when used in accordance with the conditions defined in the SmPC. The validation of the manufacturing process has been satisfactorily demonstrated ensuring the manufacturing process for Enflonsia is capable of consistent and robust performance. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. Adventitious agents safety including TSE have been sufficiently assured.

In conclusion, based on the review of the data provided, the marketing authorisation application for Enflonsia is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The nonclinical pharmacology program conducted in support of the development of clesrovimab or MK-1654 involves a panel of in vitro studies as well as one in vivo study.

The **affinity and in vitro neutralization potency** of clesrovimab and its parental, i.e. without YTE mutations in the Fc region, antibody RB-1 were evaluated by surface plasmon resonance and an in vitro neutralization assay (Study PD001).

K_D values for binding of clesrovimab to RSV pre- and post-fusion F protein were 71 pM and 480 pM. For RB-1 respective K_D values were 31 pM and 410 pM.

Clesrovimab and RB-1 were evaluated for their ***in vitro*** **neutralization potency** against the RSV A Long strain and the RSV B Washington 18537 strain in an in vitro infection neutralization assay with Hep-2 cells. The neutralization potency of Clesrovimab was determined at IC_{50} (half maximal inhibitory concentration) values ranging from 0.8 to 11.6 ng/mL for RSV strain A and from 0.5 to 5.2 ng/mL for RSV strain B. IC_{50} values for RB-1 ranged from 2.9 to 7.2 ng/mL for RSV strain A and from 0.8 to 9.0 ng/mL for RSV strain B. Thus, the in vitro neutralization potency was similar for both antibodies. Palivizumab was included in the in vitro assays for comparative purposes and was found to be clearly less potent than clesrovimab and RB-1 as expressed by IC_{50} values of 211.5 ng/mL for RSV strain A and 165.9 ng/mL for RSV strain B.

As in vitro infectivity is evaluated using an anti-RSV F fusion protein mAb and an anti-RSV nucleocapsid mAb the Applicant performed an experiment to demonstrate that RB-1 does not interfere with the detection of infectivity. For this purpose, two different lots of the RSV A strain were detected either with anti-F and anti-N mAbs or with anti-N alone. The range of IC_{50} values was similar for both approaches so that detection of infectivity with anti-N mAbs only appears valid.

In order to demonstrate that **clesrovimab and palivizumab bind different epitopes** in the RSV pre-fusion F protein, i.e. a region in site IV and site II, respectively, a comparative binding assay with an F-protein mutated in site II was performed. As a result, palivizumab did not bind to the mutated but only to the unchanged F-protein whereas clesrovimab bound to both variants of F-protein with a similar EC_{50}.

Potential **competitive binding of RB-1 and palivizumab** to the pre- and post-fusion F protein was evaluated in a sensor chip coupled with palivizumab. RB-1 was able to bind to pre- and post-fusion F protein bound to palivizumab indicating no binding competition.

To confirm that no **antagonism** can be expected **between clesrovimab and palivizumab** a combination of both mAbs was tested in an in vitro neutralization assay. In this assay fixed IC_{50} concentrations of either antibody combined with increasing concentrations of the respective second antibody were used. As a result, no inhibitory effect was detected from either antibody when compared to the use of the antibodies separately. Rather a synergistic effect in terms of virus neutralization was observed.

The **binding epitope of clesrovimab** was determined by generation of a mutation library of surface exposed residues of the RSV F protein where every residue of interest was individually mutated (Study

PD003). Loss of antibody binding was determined for RB-1 and revealed two residues critical for binding, i.e. arginine 429 and isoleucine 432. This protein-antibody interaction was confirmed by creation of co-crystal structures that revealed the interacting regions of RSV F protein and RB-1.

The **diversity of the clesrovimab binding epitope** in clinical RSV isolates was assessed in 15,527 sequences published in GenBank (Study PD004). The binding epitope was found to be fully conserved in 99.8% of the investigated sequences. In total, 13 clesrovimab epitope variants were identified. Of all sequences in the database 100% were conserved at the arginine 429 residue in the F protein proven critical for clesrovimab binding. Serine at 443 plays an essential role in viral escape of RSV A and RSV B monoclonal antibody resistant mutants (MARMs) and appeared to be conserved in >99.9% of all examined sequences. To a similarly extent the G446E mutation was identified in RSV A MARMs.

In vitro inhibition assays were performed with 47 **clinical isolates** including RSV A and RSV B subtypes sampled from different geographical regions in different years (before 2016; Study PD004). The fusion glyocoprotein was sequenced for 46 samples which demonstrated that the samples were phylogenetically diverse. The in vitro neutralization potency of clesrovimab for these clinical isolates resulted in mean IC_{50} values of 3.71 ng/mL against RSV A isolates (range from 0.46 to 11.11 ng/mL) and 4.46 ng/mL against RSV B isolates (range from 0.58 to 29.65 ng/mL). In an additional set of 12 clinical isolates sampled from 2016 to 2021 IC_{50} values determined for clesrovimab were 18.35 ng/mL for RSV A strains (range from 8.79 to 27.74 ng/mL) and 18.96 ng/mL for RSV B strains (range from 14.22 to 22.92 ng/mL). Thus, the efficacy of clesrovimab 18.96 ng/mL for RSV B appears to be higher against isolates dating back to before 2016 as compared to more recent isolates.

In a serial infection assay the tendency of a selected RSV A strain to **develop viral resistance** to clesrovimab was investigated (Study PD004). 4 RSV A MARMs were identified that proved to have mutations in the epitope region of clesrovimab and therefore could not be neutralized by either clesrovimab or its parental antibody. However, the viral fitness of these MARMs was claimed to be reduced. A corresponding experiment leading to similar results was conducted with an RSV B strain virus.

Potential **cytokine release** induced by clesrovimab was analysed in an in vitro cytokine release assay with plate-bound antibodies and antibodies in solution in PBMCs and whole blood from healthy donors (Study PD005) as well as with antibodies in solution in whole blood (Study 007). Stimulatory anti-CD3 and anti-CD28 antibodies were used as positive control whereas trastuzumab was the negative control. When considering median responses across all donors in the plate-bound assay with PBMCs no stimulation of cytokine release was observed for clesrovimab. In the whole blood assay stimulated in solution (Study PD005) median values for some cytokine subsets, i.e. IL-1β, IL-6 and IL-8, were elevated up to 7-fold over the trastuzumab controls and were in the range of positive controls at comparable antibody concentrations. In contrast, the whole blood assay of Study PD007 did not result in elevated cytokine levels triggered by clesrovimab.

The **in vivo efficacy** of the parental antibody RB-1 (MK-1654) was determined in a cotton rat model that proved relevant for the PK and efficacy evaluation of other RSV antibodies. The use of the parental antibody was justified by the fact that the YTE modification leads to increased binding to the rodent FcRn which, in turn, reduces the overall exposure to the Ab. The study was conducted comparatively with palivizumab and D25, an anti-RSV Ab that exhibits a 100-fold higher in vitro potency than palivizumab and is directed against a different RSV epitope than RB-1.

A pilot study (RSV-118) investigating the lung efficacy against RSV strain A2 (EC_{50}) was conducted where rats received doses of 0.025, 0.25, 2.5, and 5 mg/kg RB-1 or palivizumab, or 0.125, 1.25, and 2.5 mg/kg of D25. One day after immunization animals were challenged intranasally with 1×10^5 plaque-forming units of the RSV A2 strain. At termination four days after challenge EC_{50} values were 1.719 µg/mL, 1.056 µg/mL and 6.940 µg/mL for RB-1, D25 and palivizumab, respectively, where EC_{50}

is the effective concentration in reducing 50% of the viral load after RSV A challenge. Thus, RB-1 and D25 appear to be of comparable efficacy whereas palivizumab is less effective.

The objectives of the main study (RSV-128) were to determine the effective concentration of RB-1 and D25 for reducing 90% (EC_{90}) or 50% (EC_{50}) of the viral load in the lung and nose after RSV A and RSV B challenge. Antibody doses were 2.5, 0.83, 0.28, 0.09, 0.03 mg/kg. The challenge protocol was identical with that of the pilot study RSV-118.

As a result, EC_{90} values of RB-1 and D24 were similar against RSV A in the lung (10.3 and 11.8 µg/mL) whereas corresponding EC_{50} values showed approximately double the efficacy of RB-1 than D25 (1.1 µg/mL and 2.7 µg/mL). In the nose EC_{50} for RB-1 (9.9 µg/mL) was approximately double that of D24 (4.2 µg/mL). As for EC_{90} RB-1 was also less effective than D25, however the relative multiplicity was less than for EC_{50} (22.6 and 16.1 µg/mL).

Against RSV B RB-1 was effective in the lung as D25 as expressed by EC_{50} and EC_{90} values (6.4. and 12.8 µg/mL as well as 1.9 and 4.1 µg/mL). In the nose, the efficacy was more pronounced and resulted in EC_{50} values of 8.5 µg/mL and 25.7 µg/mL for RB-1 and D25, respectively. EC_{90} values were 20.4 µg/mL and >50.0 µg/mL for RB-1 and D25.

Efficacy data (pfu/g tissue) and antibody titers measured at day 1 after immunization were correlated and showed a > 2 log reduction of lung titers for RSV A and B strains.

In an additional study (RSV-159) the Fc effector function of the parental antibody RB-1 was evaluated. Therefore, RB-1 was engineered with a modified Fc region other than clesrovimab, namely constituted of amino acid substitutions in L234A and L235A (LALA). Clesrovimab and RB-1 LALA were administered at doses of 0.03, 0.09, 0.28, 0.83, or 2.5 mg/kg to cotton rats. Challenge with 1×10^5 pfu RSV strain A2 followed on the day after immunization. Efficacy in lung and nose as expressed by IC_{50} values was similar for both antibody variants. Therefore, Fc function is considered of minor significance in this animal model.

2.5.2.2. Secondary pharmacodynamic studies

Binding of therapeutic antibodies to erythrocytes and/or thrombocytes as a **secondary pharmacodynamic effect** can induce drug-related hemolysis or shortened platelet life span.

In order to exclude hematotoxicity directly related to potential unspecific binding of clesrovimab an in vitro assay with human and rhesus monkey red blood cells and platelets was conducted. Anti-HER-2 (trastuzumab) and PCSK9 were included as negative controls. For this purpose mAbs were labelled with DyLight™ and incubated with human or rhesus monkey whole blood. Human blood was additionally labelled with the red blood cell marker CD235a and the platelet marker CD42a. Monkey cells were differentiated by their forward scatter – side scatter characteristics.

As a result, unspecific binding of clesrovimab to human and rhesus monkey red blood cells and thrombocytes was demonstrated to be similar to the binding characteristics of anti-HER-2 and PCSK9 and, thus, of no specific concern based on the provided data.

2.5.2.3. Safety pharmacology programme

As laid down in ICH guideline S6(R1) no **safety pharmacology** studies are warranted for antibodies directed against exogenous targets. Therefore, no stand-alone safety pharmacology studies were performed for clesrovimab. However, a FOB was included in a 2-week IV and IM GLP toxicity study with a 4-week recovery period. Potential effects on the nervous system were evaluated 1 h after the

first IV dose. Additional functional endpoints, i.e. cardiovascular and respiratory, were evaluated throughout the study period. Results are supplemented by histologic tissue analysis.

2.5.2.4. Pharmacodynamic drug interactions

No studies investigating pharmacodynamic interactions have been submitted, which is accepted due to the specificity of clesrovimab targeting exogenous RSV antigen. Moreover, in vitro pharmacodynamic drug interaction studies of mAbs are generally not considered predictive.

2.5.3. Pharmacokinetics

2.5.3.1. Analytical methods

Various assays were qualified/validated to quantify clesrovimab in different animal models. An exploratory ECL-based immunoassay was used for Wistar Han rat plasma and rhesus monkey serum in non-GLP PK studies, both with an LLQ of 27.4 ng/mL. A validated ECL drug level assay assessed clesrovimab concentrations in rat serum for a GLP toxicology study, with an LLQ of 100 ng/mL. Additionally, a qualified LC-MS/MS assay quantified clesrovimab in rhesus monkey serum in a non-GLP formulation study, with an LLQ of 0.5 µg/mL.

An ECL assay (non-GLP) was sufficiently validated to detect anti-clesrovimab antibodies in the GLP toxicology study conducted in rats.

2.5.3.2. Absorption

The pharmacokinetics (PK) of clesrovimab were evaluated in Wistar Han rats and rhesus monkeys.

Adult male Wistar Han rats (4 animals/group, 2-month-old) were dosed IV with 3, 10 and 30 mg/kg or IM with 3 mg/kg clesrovimab. Over the dose range of 3 to 30 mg/kg IV, clesrovimab exhibited a dose-proportional increase in $AUC_{0\text{-}inf}$ indicating dose-linear PK properties ($AUC_{0\text{-}inf}$ of 352 to 3350 day x µg/mL). A bioavailability of 90.1% was reported for IM administration of clesrovimab. No C_{max} was reported but the individual animal concentration-time data was provided in the study report. Based on this table mean C_{max} was estimated for the 3 mg/kg, 10 mg/kg and 30 mg/kg IV groups as 117 µg/mL, 360 µg/mL and 1580 µg/mL. For the 3 mg/kg IM. group, mean C_{max} of 68.7 µg/mL occurred with T_{max} at 6 h. Independent of the administration route (i.e. IV or IM), clearance was comparable across doses (8.55 to 9.64 mL/day/kg), whereas volume of distribution was comparable for the 3 and 10 mg/kg groups (91.4 to 96.1 mL/kg) but much lower for the 30 mg/kg group (51.6 mL/kg). The reason for this was not commented by the Applicant. The study was conducted with an early formulation, which differs from both the Process 1 and 2 formulations.

The pharmacokinetics of clesrovimab were also investigated in adult female Rhesus monkeys (4 animals/group, 3 to 15 years old), after a single IV dose of 1, 10 or 30 mg/kg or an IM dose of 10 mg/kg. Similar to rats, clesrovimab exhibited a dose-proportional increase in $AUC_{0\text{-}inf}$ indicating dose-linear PK properties over the dose-range of 1 to 30 mg/kg in rhesus monkeys ($AUC_{0\text{-}inf}$ of 329 to 13500 µg/mL x day). A bioavailability of 94.7% was noted after IM administration. Mean C_{max} values were estimated based on individual animal concentration-time data from the study report with a C_{max} of 29 µg/mL, 292 µg/mL and 874 µg/mL at 1 mg/kg, 10 mg/kg and 30 mg/kg IV. For the 10 mg/kg IM group, a mean C_{max} of 148 µg/mL was noted with a mean T_{max} at day 2. Independent of the administration route (i.e. IV or IM), clearance (2.43 to 3.10 mL/day/kg) and volume of distribution (71.9 to 78.1 mL/kg) was comparable between doses. The PK study in monkeys was conducted with

Process 1 formulation which was the same as that used for the 2-week repeat-dose toxicity study in rats.

Half-life (t½) was not reported in any of the single dose PK studies.

Similar dosed normalized concentration-time profiles were seen when comparing the pharmacokinetics of four different formulations of clesrovimab (including Process 1 and Process 2) after IM single dose administration in adult female rhesus monkeys (4 animals/group). Additionally, other PK parameters also appeared comparable between formulations with t½ of 32.3 to 38.4 days, C_{max} of 118 to 144 µg/mL, $AUC_{0\text{-}last}$ of 4530 to 5270 day x µg/mL, $AUC_{0\text{-}inf}$ predicted of 5260 to 6430 day x µg/mL, Cl of 2.35 to 2.9 mL/day/kg and V_{dss} of 122 to 144 mL/kg for doses normalised to 15 mg/kg. No statistical comparison was made for these PK parameters.

2.5.3.3. Distribution

The biodistribution of clesrovimab labeled with DyLight™ 650 was studied in healthy female CD1 mice over 14 days following a single 3 mg/kg IV dose. For most organs, clesrovimab showed consistent organ disposition with tissue-to-blood ratios around 1.0 or less, except for the liver and lungs at Day 2 with values of 1.055 and 1.26, and the spleen and lungs at Day 14 with values of 2.08 and 1.02. The study was conducted with the same early formulation lot as the one used in the single dose PK study in rats.

2.5.3.4. Metabolism, excretion and drug interaction

Clesrovimab 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 traditional metabolism, excretion, and drug interaction studies were conducted with clesrovimab per current ICH S6(R1) guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals. No drug interaction studies were conducted with clesrovimab. This is acceptable as clesrovimab is not likely to impact expression levels of metabolic enzymes, such as cytochrome P450 enzymes, and hence, no effect is anticipated on the pharmacokinetics of concomitantly administered medications.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Stand-alone single dose toxicity studies with MK-1654 have not been conducted. However, toxicity after single dose exposure after IV and IM administration can be assessed as part of the repeat-dose toxicity studies conducted in rats. Assessment is conducted as part of the respective studies, please refer to the respective section in this report.

2.5.4.2. Repeat dose toxicity

The conducted repeat-dose toxicity study aimed to determine the potential toxicity, immunogenicity, and pharmacokinetic (TK) profile of clesrovimab when administered intravenously (IV) every 3 days for 13 days (total of 5 doses) and the reversibility of any changes during a 4-week treatment-free period. It also assessed the potential nervous system effects after the first IV dose and the local tolerance of clesrovimab when administered intramuscularly (IM) on Study Days 1 and 13 (total of 2 doses).

Four groups of Wistar Han rats received IV doses of 0, 30, 100, or 300 mg/kg/dose. Two additional groups received IM doses of 0 or 25 mg/dose. Toxicity was assessed based on mortality, clinical observations, body weight, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations.

All animals survived until the scheduled termination. There were no clinical signs, changes in body weight, food consumption, ophthalmic examinations, or clinical pathology in any group. In IV-dosed rats, there were no organ weight changes or histological findings related to clesrovimab. In IM-dosed rats, minimal inflammation and lymph node enlargement were observed, which resolved completely after the treatment-free period.

Exposure in female rats was slightly lower compared to male rats, after both IV and IM administration at all dose levels. However, differences were not regarded substantial by the applicant and not associated with any sex-dependent adversities or differences in the safety profile of animals. Thus, further calculations including safety margins were based on sex-combined mean exposure levels. Mean serum clesrovimab C_{max} values on Study Day 1 were approximately dose proportional, while mean $AUC_{0\text{-}72h}$ and C_{max} values were generally less than dose proportional on Study Day 13, with mean C_{max} values following repeated doses that were slightly higher (1.2- to 1.6-fold) than those attained on Study Day 1. The mean apparent terminal $t_{1/2}$ ranged from 259 to 359 h (i.e., 11 to 15 days) following dosing on Study Day 13.

Findings were noted in the biochemical parameters including slight but statistically significant increases in total protein in the 300 mg/kg group (M/F) and albumin (at doses of 30, 100 and 300 mg/kg in males and 100 and 300 mg/kg in females) at Day 12 and a decrease in globulin at doses of 100 mg/kg (M/F) on Day 42 but not in the higher dose of 300 mg/kg. The findings were not associated with changes in leukocytes counts, had no microscopic correlates and potential immunotoxicity was excluded. However, the biological relevance remains unclear.

Systemic exposure multiples at the NOAEL were >40-fold for AUC and C_{max}, thus presenting sufficient safety margins when comparing nonclinical exposure with the highest clesrovimab exposure obtained in infants administered the clinical doses of 105 and 210 mg IM in the Phase 2b/3 clinical studies.

Overall, no severe systemic changes in rats administered clesrovimab IV or IM were reported. The observed changes were minimal and fully reversible, indicating good overall tolerance of clesrovimab. The NOAEL for systemic toxicity after IV administration was ≥300 mg/kg/dose, and ≥25 mg/dose for IM administration.

2.5.4.3. Genotoxicity

Mutagenicity studies with clesrovimab have not been conducted as these studies are not required for biotechnology-derived products directed against foreign targets, according to ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Additionally, clesrovimab is an mAb directed toward an exogenous target and is not expected to cross the nuclear or mitochondrial membranes to interact with DNA or chromosomes.

The lack of genotoxicity studies is acceptable in accordance with ICH guideline S6(R1).

2.5.4.4. Carcinogenicity

Carcinogenicity studies with clesrovimab were not conducted as these studies are not required for biotechnology-derived products directed against foreign targets, according to ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

Additionally, clesrovimab binds a non-endogenous foreign virus-specific target that is not expressed in nonclinical species or in humans and is intended for a single or intermittent clinical use.

Thus, in accordance with ICH guideline S6(R1) the omission of carcinogenicity studies is considered acceptable.

2.5.4.5. Reproductive and developmental toxicity

In accordance with ICH guideline S6(R1), no dedicated studies have been conducted to evaluate the effects of clesrovimab on fertility, embryo-foetal, and prenatal and postnatal development. Clesrovimab binds a viral-specific target that is not expressed endogenously in non-clinical models or in humans, and the intended clinical population (infants and children) does not include women of childbearing potential. In addition, clesrovimab did not show any adverse effects on reproductive tissues in the repeat-dose toxicity study and did not bind to any evaluated human reproductive tissues (including placenta) in the tissue cross-reactivity study.

In the absence of adverse local or systemic effects of clesrovimab and in the absence of cross-reactivity with human tissues the omission of dedicated non-clinical fertility, embryo-foetal and prenatal and postnatal development studies is supported.

2.5.4.6. Toxicokinetic data

Toxicokinetics from the repeat-dose toxicity study in rats were assessed in the respective section of the study.

2.5.4.7. Tolerance

The local tolerance of the clesrovimab formulation was evaluated in rats through single and repeat dose studies, showing consistent well-tolerated results at the injection site. Both the commercial (150 mg/mL) and clinical trial (100 mg/mL) formulations demonstrated good local tolerance, supporting their use at the site of administration.

2.5.4.8. Other toxicity studies

In the 2-week repeat-dose toxicity studies in rats, clesrovimab showed no hypersensitivity or anaphylaxis, with immunogenicity (ADA response) observed only at a low dose in one rat, which is a common observation with biopharmaceuticals.

Two dedicated studies on evaluation of tissue-cross reactivity were conducted with clesrovimab. The studies evaluated the potential tissue cross-reactivity of clesrovimab with various normal human tissues, including lung and reproductive tissues, as well as normal human adult, juvenile, and neonatal tissues, at different concentrations. While positive controls showed staining as expected, negative controls did not show specific staining, confirming the assay validity. The test article clesrovimab did not produce specific staining in any of the tissues tested, whether adult, juvenile, or neonatal. Minimal increases in interstitial macrophages and dendritic cells in the kidney and pancreas were observed but were not considered toxicologically significant. Overall, clesrovimab did not show specific staining in the evaluated tissues, indicating no significant adverse cross-reactivity.

Immunotoxicity evaluation was integrated in the routine repeat-dose toxicity study.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has provided an acceptable justification for not conducting a full Environmental Risk Assessment. Since clesrovimab is a monoclonal antibody with effect on the prefusion conformation of the respiratory syncytial virus F protein, it is expected to be fully metabolized into small peptides and amino acids via catabolic pathways in the body with negligible excretion of intact, biologically active protein. In accordance to the guideline (EMEA/CHMP/SWP/4447/00 corr 21*), clesrovimab is therefore considered to be of no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Clesrovimab (MK-1654) is an extended half-life YTE-modified fully human monoclonal antibody (mAb) directed against the epitope in site IV of the RSV fusion (F) protein to prevent viral entry into cells. It is indicated as a preventative measure, providing passive immunity against RSV-associated lower respiratory tract infection in infants for the duration of a season.

The scientific rationale behind clesrovimab was to identify and develop a neutralising mAb that via its variable region potently binds a novel bindings site in a globally highly conserved RSV F protein epitope, and further to modify its Fc region for higher affinity towards the neonatal Fc receptor (FcRn) to markedly extend antibody half-life. The Fc modification is thought to also reduce binding to FcRγ expressed by innate immune cells, minimising engagement that could lead to undesirable activation of the immune system. This approach has previously been successfully carried out during the developmental programme for another anti-RSV humanised mAb.

The mechanism of action for clesrovimab is largely demonstrated using in vitro binding assays, in vitro infection neutralisation assays, and in vivo neutralisation studies in cotton rat challenged with intra-nasally administered phage units of RSV A and B strains.

Binding characteristics of clesrovimab were evaluated in terms of determination of K_D values as well as of the neutralization potency. The binding affinity to the pre-fusion F protein was clearly higher than to the post-fusion protein, confirming the therapeutic target of clesrovimab. A thorough characterization of the binding epitope on the RSV F protein was performed by establishing a mutation library of relevant residues followed by investigating loss of Ab binding. The interaction of clesrovimab with the RSV F protein was in addition verified by co-crystallization.

Binding site mutation of site II and competitive binding assays verified that clesrovimab and palivizumab bind to two separate epitopes of the F protein, i.e. site IV and site II, respectively.

The Applicant's approach to investigate the degree of conservation of the critical binding epitope in 15,527 sequences is considered important in terms of confirmation that the mutation frequency in that epitope is very low and the development of MARMs occurs to a very low degree. In addition, the development of MARMs under selective pressure was investigated. The Applicant performed an in vitro experiment to investigate the tendency of RSV A and B strains to develop MARMs under selective pressure, i.e. presence of clesrovimab. A total of five MARMs were identified after serial in vitro infection. Mutations appeared to be located in the binding epitope at site 443 (S443P) and/or site (G446E). In order to justify the postulated decreased viral fitness of MARMs selected under the pressure of clesrovimab the Applicant provided the results of an in vitro competition experiment with the RSV-A WT strain and G44E/W variants demonstrating a significant decrease of the proportion of the variants over a number of passages. In clinical studies RSV variants with substitutions in the clesrovimab binding epitope were rare and it is to date not clear whether these variants can be

transmitted. It was further argued on the example of a study conducted with palivizumab, that resistant RSV variants appear to be less likely transmitted due to their reduced fitness. Moreover, an estimation of the percentage of resistant variants of total breakthrough infections in the case of palivizumab was at 5%. It was concluded that breakthrough infections due to clesrovimab MARMS were possible, however, not of major concern due to reduced viral fitness as compared to circulating strains.

The in vitro neutralization potency of clesrovimab against RSV A and RSV B laboratory strains was similar indicating also clinical efficacy against both RSV strains. In comparison to palivizumab, clesrovimab exceeds the in vitro neutralization potency by a multiple.

The Applicant demonstrated in an in vitro inhibition assay that clesrovimab was capable of neutralizing 59 clinical isolates of the RSV A and RSV B strain over a total IC_{50} range of 0.46 to 29.65 ng/mL. The neutralization efficacy of clesrovimab against a batch of clinical isolates dating back to before 2016 and a batch of more recent clinical isolates both containing RSV A and RSV B strains was determined in vitro. It appears that neutralization efficacy of clesrovimab against isolates collected before 2016 is higher than against those collected more recently based on the mean IC_{50} values which are 3.71 ng/mL versus 18.35 ng/mL for RSV A strains and 4.46 ng/mL versus 18.96 ng/mL for RSV B strains, respectively. It appears that especially the lower bound values of the IC_{50} range increased between the two batches. In respect to discrepancies in in vitro neutralization assays between batches of clinical isolates dating back longer and more recently collected, the Applicant argues that the differences are most likely due to changes that have been applied to the assay kit. As reference laboratory RSV strains were included in experiments with both sample batches. The difference in results between the reference strains in "early" and "late" experiments approximately reflects the difference between clinical sample batches. Therefore, the Applicant's explanation is considered conceivable.

In order to address the potential of clesrovimab to induce a cytokine release syndrome two in vitro studies with whole blood and PBMCs from healthy human donors were conducted. As a result of the in vitro assay in Study PD005 in whole blood the mean values of some cytokines (IL-1β, IL-6 and IL-8) were elevated to the range of positive controls at comparable antibody concentrations. Provided data demonstrated very high variability in untreated whole blood samples (including historical controls) covering also the cytokine levels in question, which is most probably attributable to the high inter-individual variability of donors. The difficulty in the determination of IL-8 levels correctly was specifically highlighted. It was further argued that the similarity of cytokine levels to those of palivizumab, the unlikeliness of clesrovimab to initiate a cytokine release syndrome due to structural and pharmacological properties as well as no safety concerns observed to date in the clinical studies preclude any clinical implications of the observations related to cytokines.

In an in vivo efficacy study in a cotton rat model RB-1, the parental antibody of clesrovimab lacking the Fc modifications, was demonstrated to be of similar efficacy as D25 and of higher efficacy than palivizumab in reducing the pfu of RSV A and RSV B strains in nose and after passive immunization. Moreover, by modifying the Fc region of RB-1, the Fc effector function was shown to be of limited significance for neutralization of RSV in the cotton rat challenge model.

It is unknown if competition could exist between maternal antibodies and clesrovimab for FcRn binding sites/IgG-recycling and if clesrovimab is preferentially recycled over endogenous maternal IgG due to the increased affinity for FcRn through the YTE modification thereby reducing passive immunity from maternal IgG, potentially causing the neonate/infant more susceptible to other infections than RSV. At present, clinical data does not support increased incidence of non-RSV infections, but the risk cannot be ruled out.

The YTE-modification has been described in the literature and through previous procedures to minimise FcγR binding, thus lowering the risk of innate immune cell engagement through FcRγ as well as

minimising potential antibody-dependent enhancement (ADE). While reference is made to the literature and same-in-class medicinal products containing the YTE modification, which have not demonstrated such concerns, this argument is insufficient. Due to potential Fc-Fab interactions, the Fc-mediated effects of antibodies cannot be assumed to be identical across antibodies with different complementarity-determining regions (CDRs), even when the Fc region is identically modified. Therefore, it is noted that potential ADCC and ADCP responses have not been characterized, and their contribution to the pharmacological effect remains unknown. Serious ADE responses, however, have not been reported in the clinical data with clesrovimab.

Clinical as well as laboratory batches of clesrovimab have been used for non-clinical pharmacology. On the quality level all these batches are considered comparable and therefore no restraints regarding the validity of the data generated exist.

As laid down in ICH guideline S6(R1) no **safety pharmacology** studies are warranted for antibodies directed against exogenous targets. Safety pharmacology endpoints were evaluated as a part of the 2-week repeat-dose toxicology study in male Wistar Han rats using a functional observational battery (FOB). However, seeing that the target is not expressed in the uninfected rat and, additionally, that the rat is not considered an appropriate animal model, the predictive value of the FOB data is limited. Thus, potential safety concerns must be evaluated in a clinical setting in the presence of an RSV target and in a relevant population. The absence of a hERG study was sufficiently justified based on the scientific review by Vargas et al, 2008, stating that no changes were noted for cardiovascular and respiratory endpoints assessed via routine clinical observations and comprehensive histopathological examination.

Pharmacokinetics

Two ECL-based immunoassays for the determination clesrovimab concentrations and ADA's have been validated in support of the pivotal repeat-dose toxicology study in rat. Clesrovimab concentration was quantifiable between the range of 100 ng/mL and 6400 ng/mL. Samples of 5,000,000 ng/mL was securely diluted up to 1/25,000 dilution, still attaining acceptable accuracy and precision. Clesrovimab was demonstrated stable at room and refrigerator temperatures for up to 19 hours and at -80°C and -20°C for LOQ and HQC for up to 72 days. Samples were furthermore stabile when subjected to up to 6 freeze/thaw cycles. Serum from the pivotal repeat-dose toxicology study in rat were collected and analysed within established stability limits, with a maximum time from collection to analysis of 59 days. Incurred sample analysis was successful as only one in 32 samples was found ±30% outside the original values, thus confirming reliability of the assay. The immunoassay for quantification of anti-clesrovimab antibodies had initially raised some concerns related to cut-point determination and drug tolerance, however, seeing that the ADA results from the toxicity study are not considered to have a meaningful translatability to humans nor a strong scientific value, partly due to the short study duration, these issues are not pursued further.

The pharmacokinetics of clesrovimab was evaluated in two single dose PK studies in male Wistar Han rats and in female Rhesus monkeys with both IV and IM administration.

Clesrovimab exhibited a dose-proportional increase in exposure in both species indicating dose-linear PK properties, as also seen in the clinical setting. A high bioavailability (>90%) was noted in both species with volumes of distribution of 51.6 to 96.1 mL/kg. Difference was however observed, clearance was lower for monkeys than rats (3-fold) and T_{max} appeared to be reached earlier in rats (6 h) compared to monkeys (day 2). Half-life (t½) calculations based on the single dose PK studies in rats and monkeys were considered less relevant due to the limited duration of serum concentration follow-up measurements making AUC extrapolations and hence, t½ calculations uncertain. However, based on the more reliable studies, mean $t_{1/2}$ in rats ranged from 11 to 15 days (study no. TT #16-1029) and 32 to 38 days in monkeys. Hence, t½ was considerably longer (2- to 3-fold) in monkeys than in rats.

However, it did not fully predict the prolonged t½ in adult humans of 73 to 88 days (measured) or 44 days (modelled) in infants. Thus, the YTE modification clearly prolongs half-life, but the effect is species-dependant, with the greatest extension observed in humans in line with its intended purpose.

As only male rats and female rhesus monkeys were included in the submitted studies, no gender difference could be estimated within species. However, it appears like a previous study were conducted in male rhesus monkeys, indicating similarities in concentration-time profiles between genders. However, this study report was not submitted. Nevertheless, an absence of gender differences in the monkeys correlated with clinical findings of no gender-related differences in PK profiles.

Similar dosed normalized concentration-time profiles were seen when comparing the pharmacokinetics of four different formulations of clesrovimab after IM single dose administration in adult female rhesus monkeys. Furthermore, data indicated that neither the protein concentrations (100.8 to 188.8 mg/mL) nor the addition of arginine in the formulation appeared to impact the PK profile of clesrovimab under the specific study conditions.

Biodistribution was investigated in female CD1 mice after a single IV dose of 3 mg/kg DyLight™ 650 fluorescent labelled clesrovimab (MK-1654) in a study also characterising stability and potential protein interaction. Tissue-to-blood ratios lower or approaching 1.0 were noted for most organs, except the liver and lungs at Day 2 with values of 1.055 and 1.26, and the spleen and lungs at Day 14 with values of 2.08 and 1.02. This indicated that clesrovimab tissue uptake were especially seen in the spleen, but also in FcRn high-expressing organs like lungs and liver. For most of the tested organs, clesrovimab tissue-to-blood ratios were highest at Day 14, the last time point. This makes it difficult to estimate when the peak tissue-to-blood ratios of clesrovimab were reached in different tissue compartments and when elimination is completed. Brain tissue was not examined but due to their size mAb are not expected to cross the blood-brain barrier (BBB). This is, however, not necessarily translatable to infants with a developing BBB, that could be at different risk. Placental transfer and excretion to milk was not evaluated.

In the mouse biodistribution study, clesrovimab was stable in the circulation with a chromatographic peak corresponding to intact monomeric IgG and the amount of the peak decreased over time, as a result of drug clearance and hence decreased drug concentration in plasma. No evidence of clesrovimab interacting with other proteins in mouse plasma was noted.

No additional metabolism, excretion or drug interaction studies were conducted, which is acceptable in accordance with ICH S6.

Toxicology

Overall, the toxicology program of clesrovimab revealed no major concerns. The toxicity studies supporting the marketing authorization of clesrovimab in the intended indication were performed according to appropriate ICH guidelines, taking into consideration the nature of the product being a monoclonal antibody directed at a foreign target.

The non-clinical toxicology programme consisted of a 2-week repeat-dose toxicity study in rats including both intravenous (IV) and intramuscular (IM) administration, a standalone IM local tolerance study and two human tissue cross-reactivity studies including adult, juvenile and neonatal tissues. The repeat-dose toxicity study was conducted with a process 1 formulation of clesrovimab, whereas the standalone local tolerance study was conducted with a process 2 formulation. Adequate similarities between the process 1 and 2 formulations were confirmed in a bridging study assessed in the quality section of the dossier (please see relevant parts of the quality assessment) and by similar PK concentration-time profiles in female rhesus monkeys. All pivotal non-clinical studies were conducted in accordance with OECD GLP requirements.

The antigen for clesrovimab (RSV outer membrane F protein) is not endogenously expressed in humans or any animal species. Hence, no relevant toxicological species exists for evaluation of target-mediated toxicity. The rat was chosen as the relevant animal species for the repeat-dose toxicity study, based on the rationale that systemic exposure of clesrovimab in the rats were sufficient to cover the anticipated clesrovimab exposure in humans. However, in an article by Dall'Acqua et al. (2006) the non-human primate (NHP) was flagged as the most pharmacologically representative species with respect to potential off-target toxicity due to similarities in FcRn binding and prolonged half-lives due to the triple YTE mutation. The Applicant argued that no off-target toxicity was expected due to the lack of staining in the conducted tissue cross-reactivity studies in adult, juvenile, or neonatal human tissues. Furthermore, the shorter half-life in rats compared to NHPs and humans were accounted for by an increased dosing frequency in the repeat-dose study in order to maintain a high antibody exposure relative to the clinical therapeutic dose (exposure margin of > 40-fold). It was therefore agreed that, as no relevant toxicological species exists and no off-target effects were expected in neither NHPs nor in rats, the use of the rat is supported from a 3R perspective in order to avoid unnecessary use of NHPs.

Clesrovimab appeared to be well tolerated in rats. No mortalities were seen in the conducted study and no severe adverse local or systemic effects were noted after a 4-week recovery period.

Local tolerance was assessed in a group of intramusculary (IM) dosed rats and minimal to mild treatment related injection site reaction (inflammation in the quadriceps muscle and subcutis) with regional lymphoid hyperplasia was noted. This corresponded to the expected response to injection of foreign antigens (fully human immunoglobulins) and vehicle material. In the control animals, less local injection site reaction with no effect on regional lymph nodes were observed and these findings consisted with a mild "clean-up" reaction due to injection of vehicle material into the muscle. Full recovery was seen after the treatment-free period of 4 weeks in both treated and control animals. An additional GLP compliant standalone single dose local tolerance study was conducted in Wistar Han rats with IM doses of 0 or 25 mg clesrovimab. The study was conducted with the process 2 formulation more similar to the one intended for commercial use (150 mg/ml). The lack of mild local injection reaction and regional lymph node hyperplasia, as previously seen in the repeat-dose toxicity study (TT#16-1029), indicated a better local tolerance of the process 2 formulation. NOAEL for local tolerance was 25 mg/dose.

No stand-alone immunotoxicity studies were conducted. Instead, potential immunotoxicity of clesrovimab was evaluated based on standard toxicity parameters as part of the 2-week repeat-dose toxicity study in rats in accordance with the ICH S8 (Section 2.1.1) recommendations. No evidence of immunotoxicity were seen. Furthermore, the Applicant stated that, no special cause of concern was noted based on clinical findings in the intended patient population.

No findings were noted in the neurobehavioral functional observational battery (FOB). However, the one-hour sampling time point was considered premature for excluding all potential neurobehavioral effects (please see safety pharmacology section for further discussion).

Overall, no severe adverse local or systemic effects of clesrovimab were noted in the conducted 2-week repeat-dose toxicity rat study. No changes persisted through the 4-week recovery period. The NOAELs were therefore considered to be the highest doses of 300 mg/kg IV. and 25 mg IM. This is accepted based on the presented non-clinical data.

Toxicokinetics after single and repeated IV dosing with clesrovimab was investigated as part of the 2-week repeat-dose GLP study in rats. The study showed that over the IV dose range 30 to 300 mg/kg clesrovimab exhibited an approximately dose proportional serum C_{max} after the first dose, whereas C_{max} and $AUC_{0\text{-}72h}$ were less than dose-proportional on Study Day 13 after a total of five doses. C_{max} values at Study Day 13 following repeated administration was, however, slightly higher (1.2- to 1.6-

fold) than those attained on Study Day 1. No evidence of accumulation was seen. Mean terminal half-life ($t_{1/2}$) ranged from 10.8 to 15.0 days, which is markedly shorter than observed in humans but expected due to the different YTE Fc-FcRn engagement in rodents. No significant sex-differences were seen.

Anti-drug antibodies (ADA) were detected in one female animal in the 30 mg/kg dose group from day 28 post the first dosing. Even though the individual exposure of the animal was highly diminished, suggesting strong neutralising ADA potential, no substantial impact on overall group mean concentration and toxicokinetic values were noted. It should be noted that the scientific value of anti-drug antibody (ADA) formation in animal models are limited due to the short study duration (2 weeks) and a general lack of translatability to the clinical situation. Hence, ADA formation must be further assessed in the clinical setting.

Interspecies comparison data was presented as a comparison of exposure multiple calculated based on the approximate exposure achieved over the first 3 days in the repeat-dose rat study ($AUC_{0\text{-}72h}$) over the clinical exposure over 3 days ($AUC_{0\text{-}72h}$) in infants ≥25 weeks gestational age and postnatal age 0 to 8 months after administration of 105 mg (IM) or ≥25 weeks gestational age and postnatal age 9 to 20 months after administration of 210 mg (IM). For the NOAEL of 300 mg/kg, a safety margin of >40-fold based on $AUC_{0\text{-}72h}$ and C_{max} were obtained for the two age groups in the clinical studies, which is considered sufficient.

In accordance to ICH S6 (R1) guidance stating that "For monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets etc.), a short-term safety study in one species (choice of species to be justified by the Applicant) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate", no dedicated reproductive toxicity studies have been conducted for clesrovimab. Additionally, clesrovimab did not show any adverse effects on reproductive tissues in the 2-week repeat-dose toxicity study (study no TT#16-1029) and did not bind to any evaluated reproductive tissues in the human tissue cross-reactivity study conducted in a full adult tissues panel (including cervix, uterus, ovary, fallopian tubes, placenta, testes and prostate from adults) and selected juvenile and neonatal tissues (including ovary and/or cervix). Furthermore, the intended clinical population (neonates and infants) does not include women of childbearing potential.

As clesrovimab is indicated for treatment in neonates and infants, a paediatric investigation plan (PIP) was conducted and no need for non-clinical juvenile animal studies (JAS) were described. Additionally, at the current timepoint extensive clinical data exists from the paediatric population and juvenile animal study is therefore not expected to provide any added safety value in accordance with ICH S11.

Hence, considering the nature of the target, the therapeutic modality, the absence of a good predictive animal model, the lack of severe adverse local and systemic effects in the conducted toxicity study and lack of cross-reactivity with human tissues including selected juvenile, neonatal and foetal human tissues, omission of dedicated non-clinical reproductive and developmental toxicities (i.e. fertility, embryo-foetal, and prenatal and postnatal development studies) and juvenile studies is supported in accordance to guideline. No animal data was therefore included in section 4.6 of the SmPC, which is acceptable and in line with similar previous approved products.

Two human tissue cross-reactivity studies were conducted in full adult tissues panel and selected juvenile and neonatal tissues (study No TT#15-7811 and TT#16-9012) in accordance with ICH S6 (R1) recommendations. No specific clesrovimab (MK-1654) staining was present in adult, juvenile, or neonatal human tissues in any of the two studies. In both studies, sufficient positive and negative tissues samples were included in addition to a human IgG1 isotype control. In study no TT#16-9012, differences in clesrovimab (MK-1654) staining intensity were noted in the positive controls correlating with the two concentrations used. In the toxicology written summary minimal positive clesrovimab

staining of interstitial macrophages and dendritic cell in the kidney and pancreas were reported for study no TT#15-7811 but this was not described in the study report itself. However, no similar findings were noted in the GLP compliant study (TT#16-9012) and the issue will not be further pursued.

The applicant has provided a justification for not conducting a full Environmental Risk Assessment (ERA). Since clesrovimab is a monoclonal antibody, it is expected to be fully metabolized into small peptides and amino acids via catabolic pathways in the body and only negligible amounts will be excreted to the environment. Hence, in accordance with guideline (EMEA/CHMP/SWP/4447/00 Rev. 1 – Corr), clesrovimab is therefore considered to be of no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that clesrovimab efficiently binds and neutralises RSV strain A and B so that it is suitable for passive immunisation of paediatric patients.

The CHMP is of the opinion that the submitted nonclinical PK data supports MAA for clesrovimab. The comprehensive toxicological programme conducted for clesrovimab supports the MAA. The CHMP noted though that the antigen for clesrovimab (RSV outer membrane F protein) is not endogenously expressed in humans or any animal species, and thus no relevant toxicological species exists for evaluation of target-mediated toxicity.

In conclusion, the CHMP considers that all non-clinical issues were satisfactorily solved.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Study Number/ Phase	**Study Title**	**Participants**	**Dosage and Duration**
MK-1654-001 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 non-childbearing potential N=114 clesrovimab N=38 PBO (IM or IV)	100 mg SD (IM) 300 mg SD (IM) 300 mg SD (IV) 1000 mg SD (IV) 3000 mg SD (IV) Placebo SD (IV and IM)

MK-1654-002 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 gestational age either ≥29 to 35 weeks (ie, preterm infants) or >35 weeks (ie, full-term infants), chronological age ≥2 weeks to 8 months, and weighing ≥2 kg at the time of screening	Preterm infants 20 mg SD (IM): 6 Preterm infants 50 mg SD (IM): 33 Preterm infants 75 mg SD (IM): 40 Preterm infants 100 mg SD (IM): 32 Full-term infants 100 mg SD (IM): 32 Placebo (IM): 38
MK-1654-003 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 PBO IM N=6 PBO IV	100 mg SD (IM): 6 300 mg SD (IM): 9 300 mg SD (IV): 9 1000 mg SD (IV): 9 Placebo IM or IV: 11
MK-1654-004 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	3614 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	MK-1654, 105 mg: 2411 Placebo: 1203
MK-1654-007 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	896 infants and children at increased risk for severe RSV disease	MK-1654, 105 mg: 446 Palivizumab, 15 mg/kg body weight: 450
MK-1654-008 Phase 1	An Open-label, Single-Dose Clinical Study to Evaluate the Safety and Tolerability of MK-1654 in Healthy Chinese Participants	Panel A: healthy Chinese male adults (aged ≥18 to ≤55 years) Panel B: children (aged ≥2 to ≤8 years) Panel C: infants (full-term with ≥35 weeks gestational age and	Panel A, MK-1654 105 mg: 25 Panel B, MK-1654 105 mg: 25 Panel C, MK-1654 105 mg: 25

		preterm with ≥29 to <35 weeks gestational age with a chronological age of ≥ 2 weeks (14 days) to ≤1 year (365 days)	
IM=intramuscular; IV=intravenous; N=number of participants; PBO=placebo; RSV=respiratory syncytial virus; SD=single dose			

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

PK Assay

The presented Pharmacokinetic assays to measure MK-1654 in human serum using protein precipitation, pellet trypsin digestion and analysis by LC-MS/MS were well described and established. The assays were fully validated and all measured parameters were acceptable.

Clinical pharmacology of clesrovimab has been characterized using observed data from 5 clinical trials, as well as integrated modelling and simulation results from these studies.

In Phase 1, a total of 196 healthy adult participants were enrolled (MK-1654-001 and MK-1654-003; alternative names: P001 and P003), of which 147 participants received clesrovimab as a single IM or IV dose, and 49 participants received matching placebo. In addition to study specific analyses, integrated adult popPK and PK/PD models were developed.

Integrated paediatric popPK, PK/PD, and E-R models were developed to characterize clesrovimab PK, the PK/SNA relationship, the exposure-efficacy relationship, and to evaluate the impact of intrinsic and extrinsic factors in infant participants. In the healthy infant population (MK-1654-002 and MK-1654-004; P002 and P004), PK data are available in 2446 participants that received an IM dose of clesrovimab. In MK-1654-007 (P007), the PK was characterized in 496 participants that received IM dose of clesrovimab. Of note, MK-1654-007 PK data consisted of clesrovimab concentrations from 435 participants that were dosed with MK-1654 in Season 1 (and Season 2 for those participants who continued into Season 2 dosing), as well as clesrovimab concentrations from 61 participants who were randomized in the comparator arm in Season 1 but received clesrovimab in Season 2.

The PopPK analysis was performed using NONMEM (version 7.5.1, ICON Development Solutions, Hanover, MD, USA) for nonlinear mixed-effects models. It was run on a grid of Intel Xeon servers running the RHEL 8 Linux with Altair Grid Engine (2022.1.1), GNU Fortran Compiler (Version 8.5.0), and Perl-speaks-NONMEM (PsN, version 5.3.1).

Data exploration, visualization, and simulations was performed using R® (version 4.1.3).

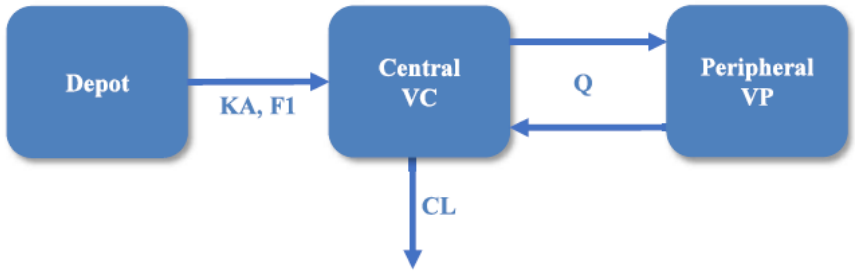
Evaluation and qualification of models

PopPK models

A preliminary two-compartment model with linear first-order elimination and first-order absorption following IM dosing was previously established using PK data from P001 (Figure 1).

Clearance and volume parameters were allometrically scaled by body weight (centered on 70 kg). IIV was included on parameters clearance (CL), central volume (Vc) and absorption rate (Ka). Residual error was described by a combined (additive + proportional) error model.

Figure 1. Schematic Structure of Population PK Model



Abbreviations: CL= clearance; F1: bioavailability; KA=absorption rate constant; Q=intercompartmental clearance; VC=central volume of distribution; VP=peripheral volume of distribution.
Notes: Allometric scaling was applied to CL, VC, VP and Q with estimated exponents.

The adult PopPK model was updated using all available adult PK data from P001 and P003. The structural model, random effect model and covariate model was re-evaluated/refined as appropriate.

The Applicant intended to develop a final population PK and a PK/PD model that describes the serum clesrovimab PK and SN titres in preterm and full-term infants from birth through their first or second RSV season.

In total, the paediatric PopPK analysis was based on 5850 samples from 2942 participants. BLQ records were mostly present one year after clesrovimab dosing, with only few BLQ samples at earlier time points. The proportion of BLQ samples depended on clesrovimab dose, with fewer BLQ samples at higher doses as expected. Most of the BLQ samples originated from study P002, since this was the study investigating the lowest clesrovimab doses.

A two-compartment structural PK model was used to fit the infant data using allometric scaling based on body weight (centered on median body weight of the P002 infant population). Informative priors for selected PK parameters (Ka and Vc, including their IIV estimates) were based on PK parameter estimates for healthy adults from a preliminary PopPK analysis of P001 study data. Allometric scaling exponents on clearance and volume parameters were estimated from the infant PK data. Bioavailability was fixed to the adult estimate. This model provided an adequate description of PK data in study P002.

As a sensitivity analysis, alternative model structures were investigated during model building (such as inclusion of an age effect on volume, or a maturation function on CL (Robbie et al, 2012; EPAR Beyfortus). None of these led to a considerable improvement in the model fit.

The previously described model developed using infant data from study P002 was used as a starting point for the analysis. Given the additional data provided from studies P004 and P007, initial modelling attempts were based on paediatric data only, not using any prior information from the adult model. However, ultimately prior information from the adult model was used for Ka and Vp, using the FOCE INTER method. The structural model and the random effects model were re-evaluated, as well as the covariate model.

Since only intramuscular PK data were available for infants, apparent clearance and volume parameters were estimated.

The infant base model included allometric scaling effects (centered on a reference body weight of 5 kg) on clearance and volume parameters, using time-varying body weight to account for rapid growth in infants. Both estimated and fixed standard allometric exponents for clearance and volume parameters were explored. In addition to time-varying body weight, the impact of a maturation function on CL based on postnatal age and gestational age, similar to what was reported for palivizumab (Robbie et al, 2012) and nirsevimab (EPAR Beyfortus), was explored as follows:

$$CL_{i,t} = TVCL * (\frac{WT_{i,t}}{WT_{ref}})^{\theta 1} * (1 - (1 - \beta_{CL}) * e^{-\left(PAGE_i - \frac{40}{4,35}\right) * \frac{\ln(2)}{T50CL}}) * e^{\eta_{CL}}$$

where $CL_{i,t}$ is individual clearance at a specific time, *TVCL* is the population typical value for clearance, $WT_{i,t}$ is individual body weight at a specific time, WT_{ref} is the reference body weight, $\theta 1$ is the allometric scaling exponent for clearance, β_{CL} denotes the fractional difference in CL of a full-term infant at birth (GA 40 weeks) compared with complete maturation, $PAGE_i$ is individual postmenstrual age in months (calculated as the sum of gestational age and postnatal age), *T50CL* is the maturation half-life for clearance, and η_{CL} is the unexplained variability from the typical value. Note that in the current analysis, the time-varying adjusted age (postnatal age + gestational age 40 weeks) was substituted by an equivalent variable ($AGEADJTV_i$) in the source dataset. Based on prior experience, a model with an effect of age on volume was also explored.

The absorption of palivizumab was ~3x faster in paediatric patients than in healthy adults (Robbie et al, 2012), whereas absorption of nirsevimab in infants was assumed to be identical to that in adults (EPAR Beyfortus). For a final model requiring a strong prior to inform Ka of infants, a sensitivity analysis was planned to evaluate goodness of model fit with differing values of Ka.

Other infant covariates were explored, and are presented in Table 1. If any of the structural parameters of the infant model were only informed by prior information from the adult model, covariates were not tested on this parameter.

Table 1. Planned Covariate Analysis in Infant PK model.

Covariate	PK Model			
	CL/F	Vc/F	Q/F	Vp/F
Body weight*	X	X	X	X
Sex	X	X		
Race	X	X		
Ethnicity	X	X		
CLD	X			
CHD	X			
Gestational age	X			
Postnatal age	X	X		
Adjusted age	X	X		
ADA	X			

Notes: Gestational age was expressed in weeks. Adjusted age was derived by postnatal age + gestational age 40 weeks. For random effect parameters where η-shrinkage did not exceed 30%, correlation plots showing the relationship between random effects and covariates were used as an explorative assessment guiding the formal covariate assessment.

* The effect of body weight on CL, Vc, Q, and Vp was part of the base structural model as described above.

Abbreviations: ADA, anti-drug antibodies; CLD, Chronic liver disease; CHD, Coronary heart disease

For the infant population, some covariates (body weight, and any age-related variables) were initially included as time-varying variables due to the rapid growth in infants over the study duration. If significant, it was evaluated if the time-varying variable could be replaced by the baseline variable without impairing model fit. Time varying covariates were evaluated as discrete measurements over time.

Table 2. Final Model Parameter Estimates for Clesrovimab PK in Infants

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]
βCLa	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 Asiana, d	-5.85	11.7		[-7.19 - -4.51]
Race effect on CL/F, percentage shift for Blacka, d	13.2	8.18		[11.1-15.3]
Race effect on CL/F, percentage shift for Multi-raciala, 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: run022-diagnostics-infant-poppk-mk1654-2024-07-03.html

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 $\widetilde{CL/F}$, for an individual with body weight = WTKG, adjusted age = AGEADJTV, and race=White can be calculated as follows.

$$\widetilde{CL/F} = 0.0197 \cdot \left(\frac{WTKG}{5}\right)^{0.524} \cdot \left(1-(1-0.579)\cdot e^{-AGEADJTV*\frac{\ln(2)}{20.3}}\right).$$

T50CL was originally estimated as a logarithmic value (original estimate: 3.01), but was exponentiated for the parameter table as 20.3.

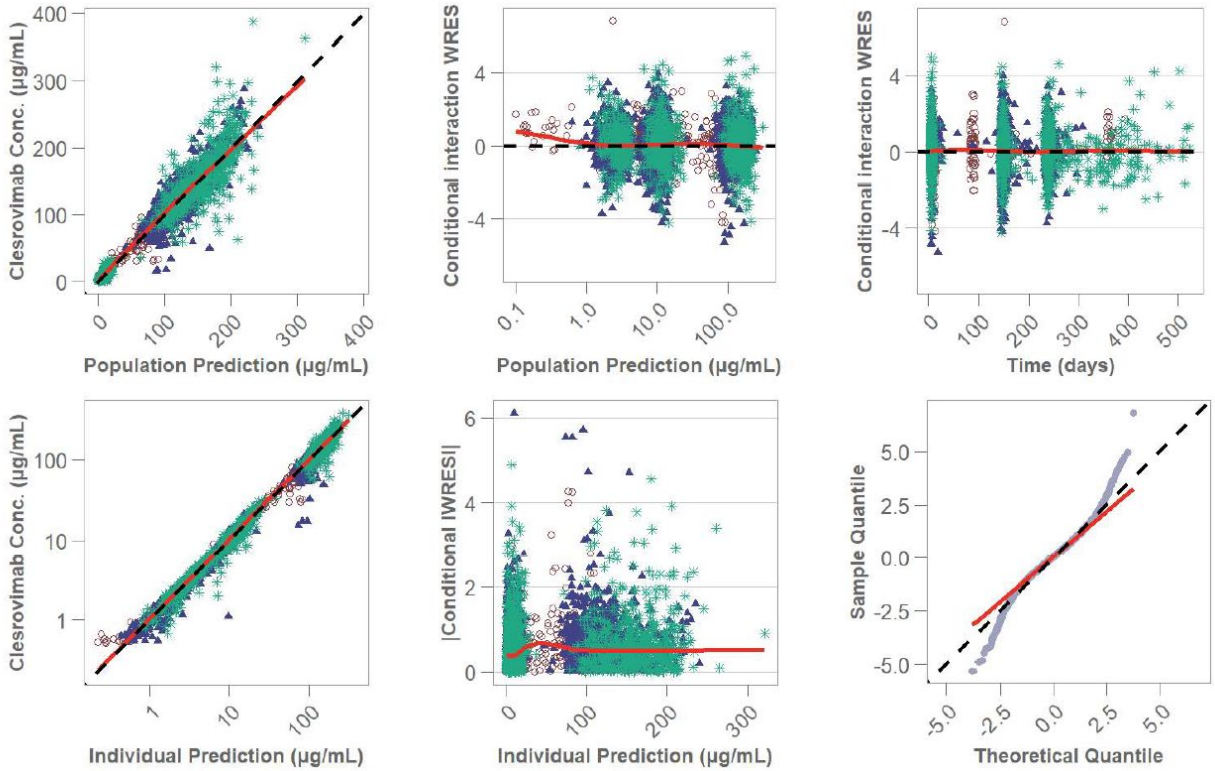
[b] The typical value of apparent inter-compartmental clearance $\widetilde{Q/F}$, for an individual with WTKG can be calculated as follows. $\widetilde{\mathrm{Q/F}} = 0.0406 \cdot \left(\frac{WTKG}{5}\right)^{0.524}$.

[c] The typical values of apparent volumes ($\widetilde{Vc/F}, \widetilde{Vp/F}$) for an individual with a body weight of WTKG were as follows. $\widetilde{\mathrm{Vc/F}} = 0.514 \cdot \left(\frac{WTKG}{5}\right)^{0.662}$, $\widetilde{\mathrm{Vp/F}} = 0.316 \cdot \left(\frac{WTKG}{5}\right)^{0.662}$.

[d] Race effects were expressed as percent difference relative to the typical estimate of the reference population (lumped category of White, American Indian/Alaskan Native, Native Hawaiian/Other Pacific Islander and Missing Race). Reference race is White.

Abbreviations: add.=additive; β_{CL}= fractional change in clearance; CI=confidence interval; CL=clearance; CV%=percent coefficient of variation; IIV=inter-individual variability; Ka=absorption rate constant; PK=pharmacokinetic; prop.=proportional; Q=inter-compartmental clearance; RSE=relative standard error; RSE%=percent RSE; Vc=central volume of distribution; Vp=peripheral volume of distribution; T50CL= maturation half-life for clearance; WTKG=time-varying body weight in kg

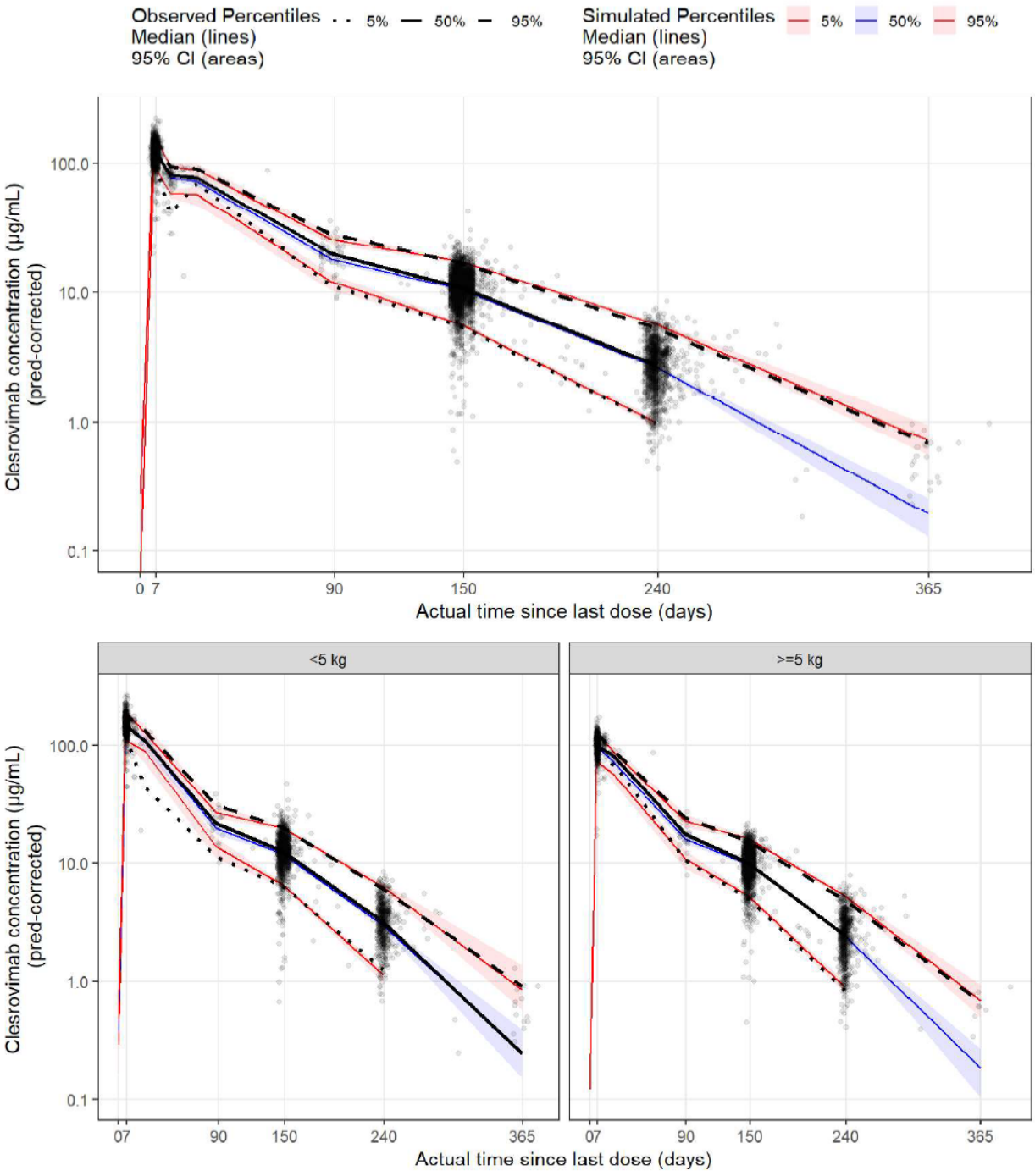
Figure 2. GOF Plots for the Clesrovimab Final Model in Infants



Notes: Dots are individual data points, with empty red circles, filled blue triangles and green crosses representing records from P002, P004 and P007, respectively. Solid red lines are smoothed LOESS lines. Dashed black lines are included for reference to indicate zero or line of unity.

Abbreviations: Conc=Concentration; GOF=goodness-of-fit; IWRESI= weighted interaction individual residuals; LOESS=locally weighted scatterplot smoothing; WRES= weighted residuals

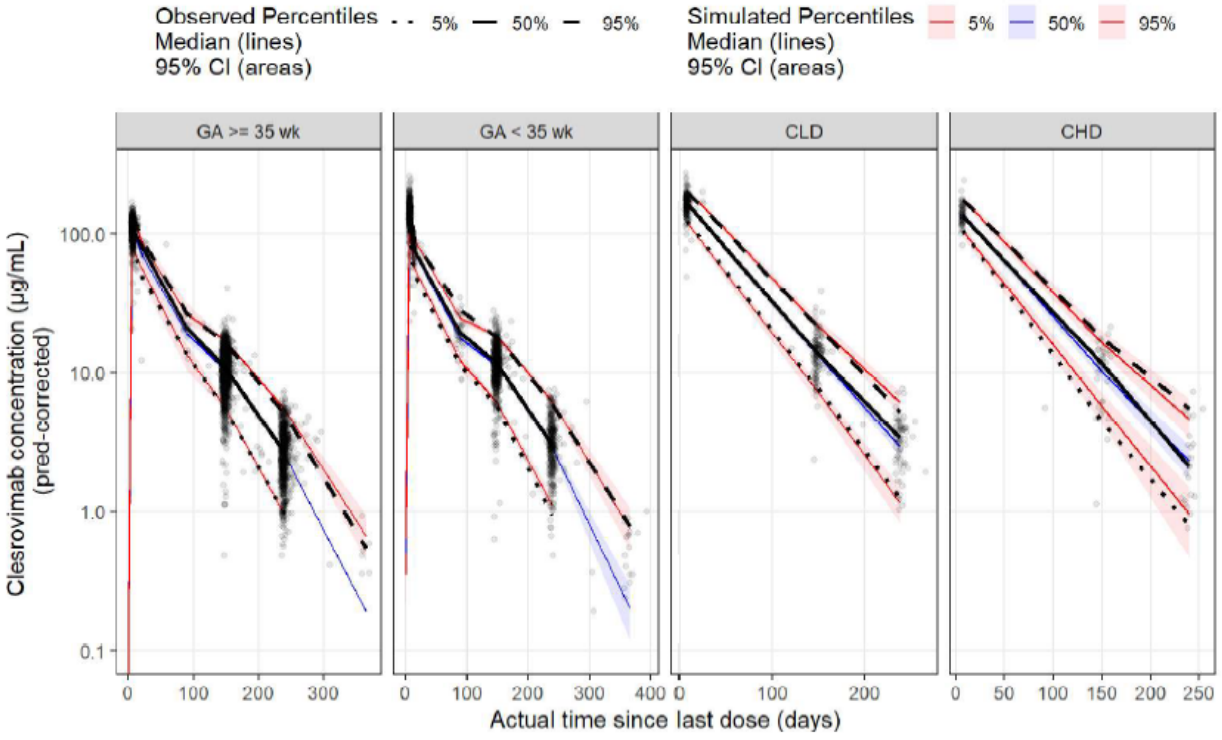
Figure 3. Prediction-Corrected VPC for Clesrovimab in Infants



Notes: Top plot shows complete population, while bottom plot was stratified by body weight. Body weight strata were defined using body weight at baseline.

Abbreviations: CI=confidence interval; pred=prediction; VPC=visual predictive check

Figure 4. Prediction-Corrected VPC for Clesrovimab in Infants by Risk Status



Source: run022-vpc-infant-poppk-mk1654-2024-07-02.html

Abbreviations: CI=confidence interval; pred=prediction; VPC=visual predictive check

Paediatric PK/PD model

Natural SN titer time-courses in infants have been described in the literature (Maas et al, 2021). These results indicated that a constant baseline after birth does not provide an adequate fit to the data. Instead, baseline SN titers were shown to vary with changes in gestational and postnatal age. Full-term infants at birth had a similar level of anti-RSV SN titers to adults due to placental transfer of anti-RSV antibodies. The SN titer declined after birth and reached a nadir at around 6 months, after which SN titers started to rebound and return to adult levels around 30 months after birth as immunity matured due to natural infection. Preterm infants had a slightly different SN titer trajectory after birth with lower initial SN titers due to incomplete maternal transfer.

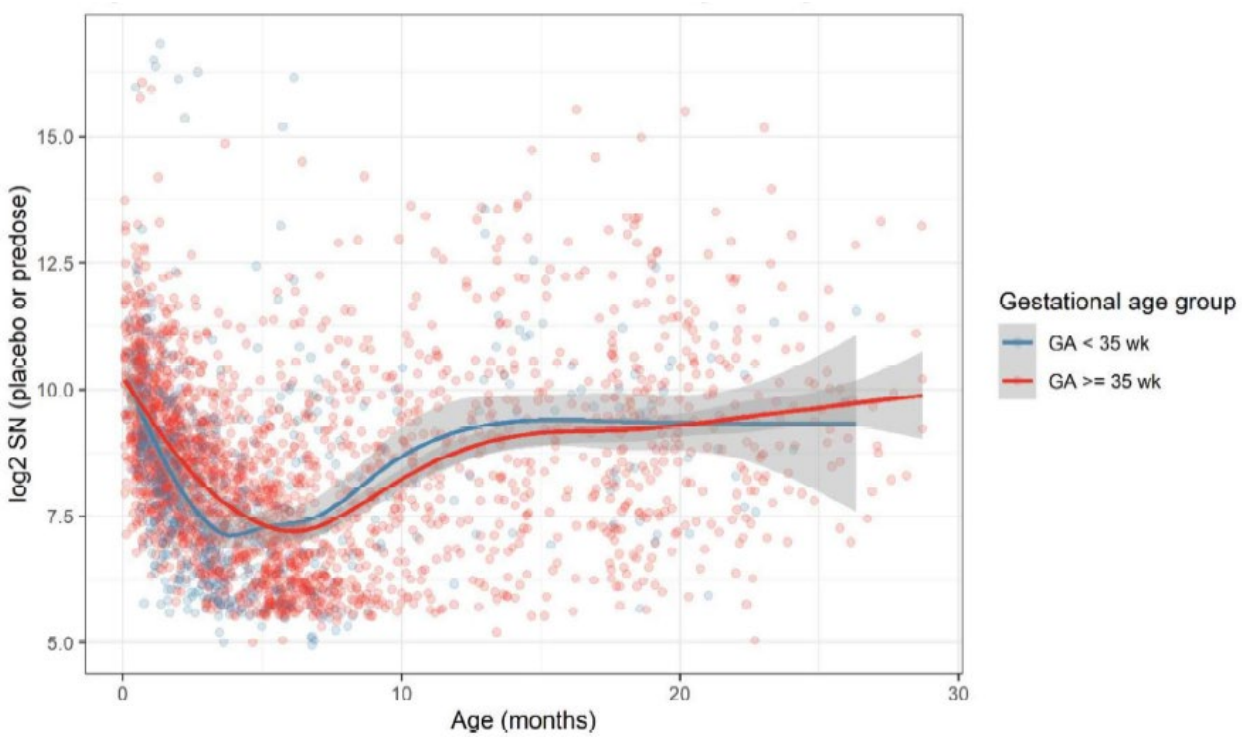
Preliminary investigations were also performed on SN titer data from study MK-1654-002. Exploratory analysis showed that baseline SN titers varied with changes in postnatal and gestational age. Titers declined after birth over the course of the observation period, while the rebound as described in the literature was not apparent in MK-1654-002 data, which might be because part of this study was conducted during the COVID-19 pandemic and RSV seasonality may have been disrupted. Full-term infants tended to have higher SN titers than preterm infants with same postnatal age.

In an exploratory population PK/PD model, a direct response model as described above for adults also provided reasonable fit to the infant SN titer data from study MK-1654-002 after including an exponential decline function on SN baseline titer as a function of postnatal age. In this model, an additional effect of gestational age was not supported based on statistical criteria.

The natural time course of SN titers after birth (Figure 9) is characterized by an initial decrease in titers, with nadir reached at 4-6 months of age. After this, average titers slowly re-increase. Similar SN

titer levels as those observed at birth are reached after approximately 15-20 months. Based on the visual assessment, there is no large difference between full-term infants, and those born prematurely. However, in infants with gestational age < 35 weeks, titers after birth seem to decrease more rapidly as compared to the more mature infants.

Figure 5. SN Titers for Placebo and Baseline Samples with Increasing Age

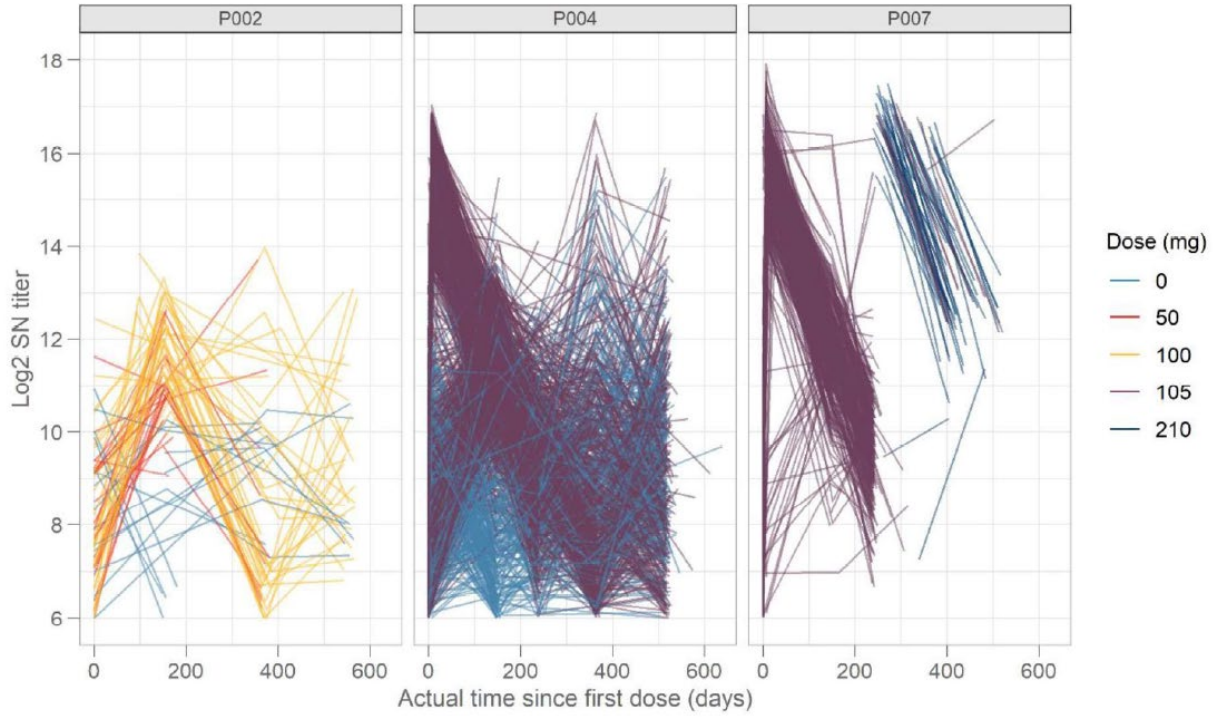


Notes: The dataset contains a large proportion of BLQ samples. The plot only shows samples above LLOQ. Therefore, the visual appearance may not necessarily reflect the true time course of SN titers with increasing age.

Abbreviations: BLQ=below limit of quantification; GA=gestational age; LLOQ=lower limit of quantification; SN=serum neutralization; wk=weeks

Figure 6 shows individual SN titer time profiles on log2 titer scale, including clesrovimab treatment arms. There was no apparent difference in titers between studies when comparing equivalent sampling time points. Within study P007, titers in the second season after a clesrovimab dose of 210 mg seemed similar to titers in the first season after a clesrovimab dose of 105 mg.

Figure 6. Individual SN Titers by Study and Dose



Source: 20240812-eda-ph3-v18.html

Notes: Maximum SN titers after a dose of 100 mg in P002 appear to be lower than maximum SN titers in P004 and P007. This apparent difference is driven by the difference in sampling time points. In P002, no SN samples were taken on day 7, while P004 and P007 included this sampling time point. Season 2 in study P007 was defined to begin with the time of clesrovimab administration, conditioned on time being later than time of first drug administration (ie a clesrovimab administration following either palivizumab or a prior clesrovimab administration).

Abbreviations: SN=serum neutralization

Table 3. Final Model Parameter Estimates for Clesrovimab PK/PD in Infants

Parameter	**Estimate**	**RSE (%)**	**Shrinkage (%)**	**95% CI**
Baseline	10.6	0.735		[10.4-10.8]
tau	4.43	2.13		[4.25-4.62]
matur	0.0879	2.45		[0.0836-0.0921]
Slope	263	1.44		[256-271]
Gestational age effect on Baseline	0.219	20.5		[0.131-0.308]
Variance (IIV Baseline)	0.0068	18.7	54.9	[0.00430-0.00930]
Variance (IIV matur)	0.0657	13.7	55.3	[0.0481-0.0833]
add. error (SD)	1.29	1.43		[1.25-1.32]

Source: run303-diagnostics-infant-pksn-mk1654-2024-07-19.html

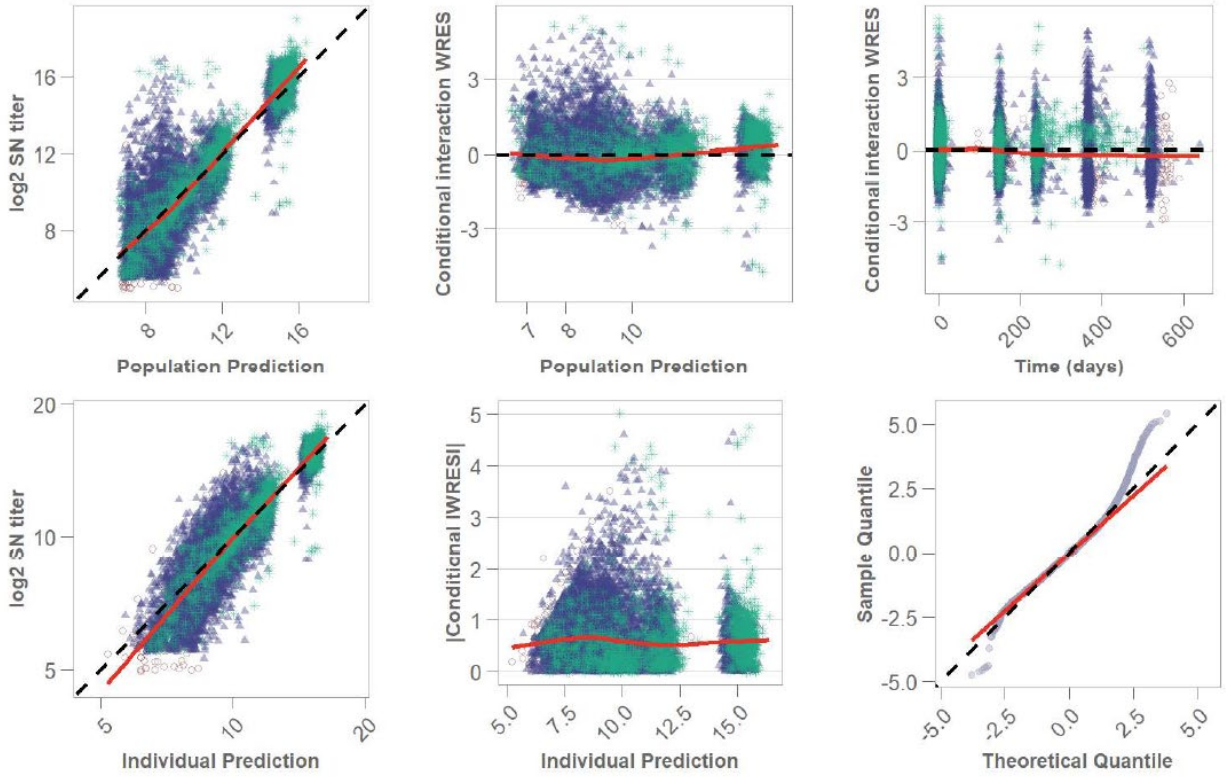
Notes: Additive residual error was implemented on log2 SN titer scale. SD for residual error calculated as $\sqrt{\sigma^2}$. IIV is presented on the variance scale. The baseline function was expressed as: $log2\ E0 = base \cdot e^{-age/tau} + base \cdot (1 - e^{-age \cdot matur})$, where *base* represents the log2 SN titers at birth, *age* is the infant age in months, *tau* represents the inverse of the rate constant of decline for innate SN titers, and *matur* represents a shape parameter describing the rebound of SN titers after 6 months of age.

The gestational age effect on Baseline ($\widetilde{Base}$) for an individual with a gestational age of GA was implemented using a power function (based on run303, see Figure 10-24):

$$\widetilde{Base} = 10.6 \cdot \left(\frac{GA}{37.57}\right)^{0.219}$$

Abbreviations: add=additive; CI=confidence interval; GA=gestational age; IIV=inter-individual variability; PK/PD=pharmacokinetic/pharmacodynamic; RSE=relative standard error; RSE%=percent RSE; SD=standard deviation

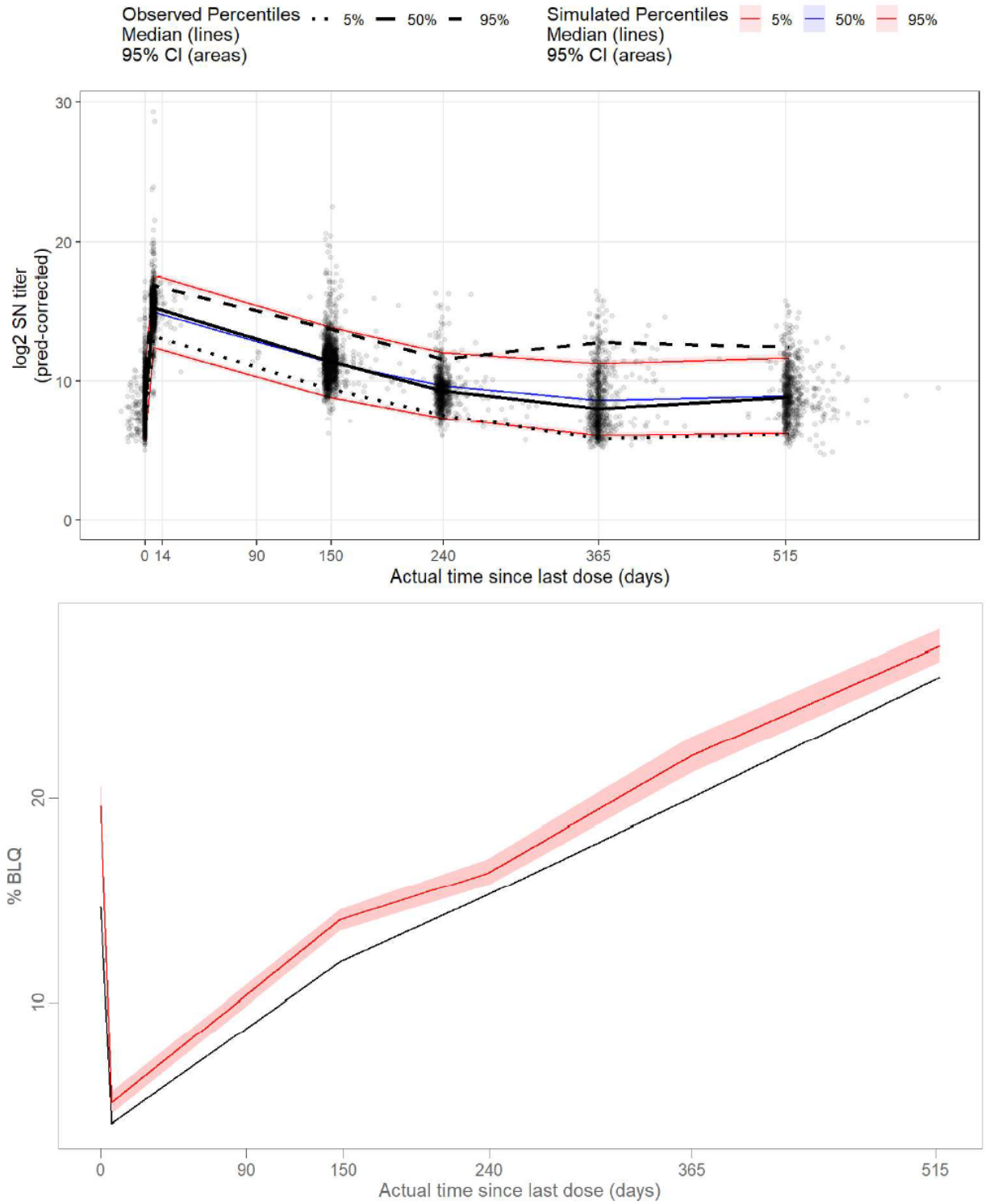
Figure 7. GOF Plots for the Clesrovimab PK/SN Final Model in Infants



Notes: Dots are individual data points, with empty red circles, filled blue triangles and green crosses representing records from P002, P004 and P007, respectively. Solid red lines are smoothed LOESS lines. Dashed black lines are included for reference to indicate zero or line of unity.

Abbreviations: DV=dependent variable (observation); GOF=goodness-of-fit; IWRESI= weighted interaction individual residuals; LOESS=locally weighted scatterplot smoothing; WRES= weighted residuals

Figure 8. Prediction-Corrected VPC for Clesrovimab PK/PD Model in Infants



Notes: The top plot shows a pcVPC for all evaluable observations. The bottom plot represents the proportion of BLQ samples within a time interval. The solid black line is the actual percentage of BLQ samples, while red line and shaded are correspond to the model-predicted percentage of BLQ samples and associated confidence 95% CI.

Abbreviations: BLQ=below limit of quantification; CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK/PD=pharmacokinetic/pharmacodynamic; SN=serum neutralization

Absorption

In the adult popPK model, IM administration to the arm resulted in 79.6% faster absorption as compared to IM administration to the thigh.

The absorption of the IM formulation was characterized by an estimated absorption rate constant (Ka) of approximately 0.286 day^{-1} (23.5% CV) based on integrated paediatric popPK model. The maximum clesrovimab concentration was estimated at a median Tmax of 6.5 days (2.5/97.5 inter-percentile range of 5.9 to 7.4 days) after IM injection.

Distribution and Metabolism

In the adult popPK model, IM administration to the arm resulted in 17.5% lower bioavailability as compared to IM administration to the thigh.

The apparent central volume of distribution (Vc/F) of clesrovimab is approximately 514 mL for a typical 5-kg infant and the apparent peripheral volume of distribution (Vp/F) is approximately 316 mL, based on the integrated paediatric popPK analysis. Therefore, the estimated apparent volume of distribution for clesrovimab is 830 mL, for a typical infant weighing 5 kg.

Clesrovimab was readily detected at the nasal mucosa of adult participants. The concentration of clesrovimab measured in the epithelial lining fluid of the nasal mucosa was 2.7% to 3.3% of the concentration measured in the serum.

As clesrovimab is a large protein consisting entirely of naturally occurring amino acids, it is metabolized through normal proteolytic pathways. Clesrovimab is administered by IM injection; hence, studies on in vitro permeability and metabolism of the drug using human biomaterials are not necessary and have not been conducted.

Elimination

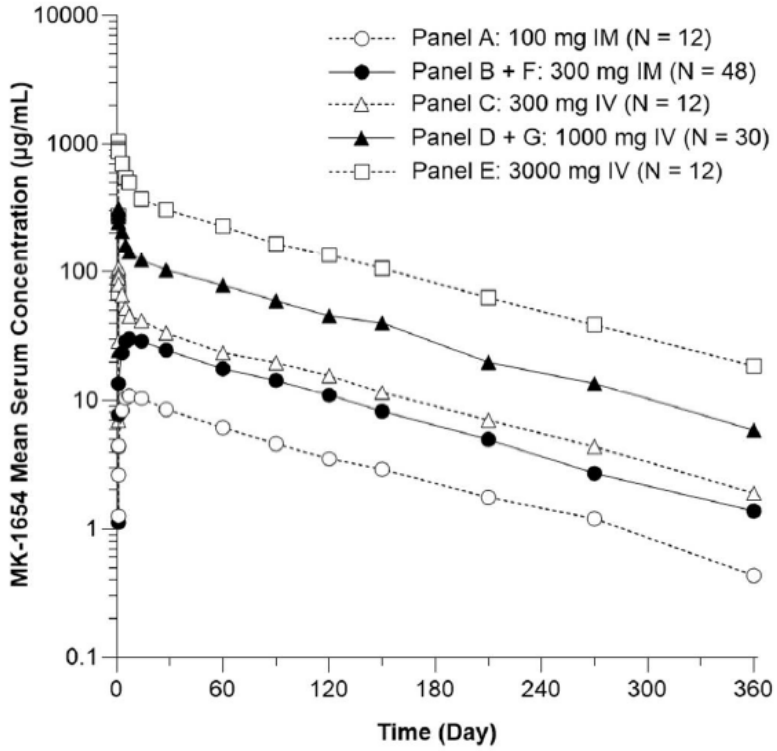
Clesrovimab is a human IgG mAb and is expected to be degraded into peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The apparent clesrovimab clearance (CL/F) was estimated at approximately 19.7 mL/day (14.4% CV) for a typical 5-kg infant. The GM of elimination half-life was 44.0 days (13.4% GCV) for infants. Adjusting for bioavailability, the estimated total clearance is 15.3 mL/day for a typical infant weighing 5 kg.

Dose proportionality and time dependencies

MK-1654-001: Mean serum concentration-time profiles for MK-1654 are provided in Figure 12. MK-1654 exhibited a biphasic PK profile. The apparent terminal elimination phases appeared to be parallel for all IM and IV panels, suggesting similar elimination t1/2 for all doses and routes of administration.

Figure 9. Arithmetic Mean (± SD) Serum Concentration vs Time Profiles of MK-1654 Following Intramuscular or Intravenous Administration of 100, 300, 1000 and 3000-mg Doses of MK-1654 as One Time Dose to Healthy Adult Participants in Panels A to E in Part 1 and Panel F to Panel G in Part 2 (Semi Log Scale) (Per-Protocol Population)



a For 1 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.

IM = Intramuscular; IV = Intravenous; N = Number of participants; SD = Standard deviation.

MK-1654-002: Due to the limited number of PK samples available for each infant, the population PK model was used to predict full PK profiles based on sparse observed data. Noncompartmental analysis was conducted on these simulated profiles to estimate serum PK parameters (Figure 13).

The Cmax and AUC0-inf of MK-1654 appeared to increase in a manner that was approximately dose proportional in preterm infants; full-term infants had approximately 20% lower exposures (Cmax and AUC0-inf) than preterm infants at the MK-1654 100 mg dose, which may be attributed to body weight differences. The GM of the apparent t1/2 of MK-1654 was 44.9 days. The GM of the apparent t1/2 of MK-1654 was generally comparable across all dose levels in preterm infants and also generally similar in preterm (range: 44.6 to 48.8 days) and full-term infants (43.0 days). The median Tmax observed across MK-1654 doses was approximately 4 days following IM administration in infants.

Figure 10. Summary Statistics of Model-Based Pharmacokinetics Parameters Following Single Dose Administration of MK-1654 (Per-Protocol Population)

Pharmacokinetic Parameters	MK-1654 20 mg			MK-1654 50 mg			MK-1654 75 mg		
	nb	GM	95% CI	n	GM	95% CI	n	GM	95% CI
$AUC_{0\text{-}Inf}$ (day*µg/mL)[a]	5	1560	(1280, 1910)	33	3530	(3270, 3820)	40	5510	(5140, 5920)
$AUC_{0\text{-}150}$ (day*ug/mL)[a]	5	1370	(1140, 1640)	33	3200	(2980, 3430)	40	4950	(4640, 5270)
Cmax (µg/mL)a	5	26.3	(22.0, 31.4)	33	61.7	(57.6, 66.1)	40	94.5	(88.8, 101)
C7days (µg/mL)a	5	24.4	(20.5, 29.0)	33	57.8	(54.0, 61.9)	40	88.1	(82.8, 93.7)
C14days (µg/mL)a	5	19.4	(16.4, 23.0)	33	46.8	(43.8, 50.0)	40	71.1	(67.0, 75.5)
C90days (µg/mL)a	5	5.60	(4.47, 7.02)	33	13.0	(11.9, 14.2)	40	20.4	(18.9, 22.1)
C150days (µg/mL)a	5	2.24	(1.63, 3.08)	33	4.98	(4.40, 5.63)	40	8.05	(7.20, 9.01)
C365days (µg/mL)a	5	0.0953	(0.0466, 0.195)	33	0.177	(0.134, 0.233)	40	0.313	(0.243, 0.403)

Pharmacokinetic Parameters	MK-1654 100 mg Preterm Infants			MK-1654 100 mg Full-Term Infants		
	n	GM	95% CI	nc	GM	95% CI
$AUC_{0\text{-}Inf}$ (day*µg/mL)[a]	32	6790	(6270, 7340)	31	5690	(5250, 6160)
$AUC_{0\text{-}150}$ (day*ug/mL)[a]	32	6120	(5700, 6580)	31	5180	(4810, 5570)
Cmax (µg/mL)a	32	117	(109, 125)	31	99.9	(93.0, 107)
C7days (µg/mL)a	32	109	(102, 117)	31	92.8	(86.5, 99.5)
C14days (µg/mL)a	32	88.6	(82.9, 94.7)	31	75.4	(70.5, 80.7)
C90days (µg/mL)a	32	25.2	(23.0, 27.5)	31	21.1	(19.3, 23.1)
C150days (µg/mL)a	32	9.70	(8.56, 11.0)	31	7.96	(7.01, 9.03)
C365days (µg/mL)a	32	0.355	(0.267, 0.470)	31	0.248	(0.186, 0.330)

a Back-transformed least squares mean and confidence interval from linear effects model performed on natural log-transformed values.

b One subject was not included because no quantifiable PK concentrations were measured post dose.

c One subject was not included because there was no PK sample collected post dose.

$AUC_{0\text{-}Inf}$ = Area under the curve from time zero to infinity; $AUC_{0\text{-}150}$ = Area under the curve from time zero to Day 150; Cmax = Maximum serum concentration; C7 = Serum concentration on Day 7; C14 = Serum concentration on Day 14; C90 = Serum concentration on Day 90; C150 = Serum concentration on Day 150; C365 = Serum concentration on Day 365.

CI = Confidence interval; GM = Geometric least-squares mean.

Clesrovimab is currently intended for one time administration only, time dependency has not been studied.

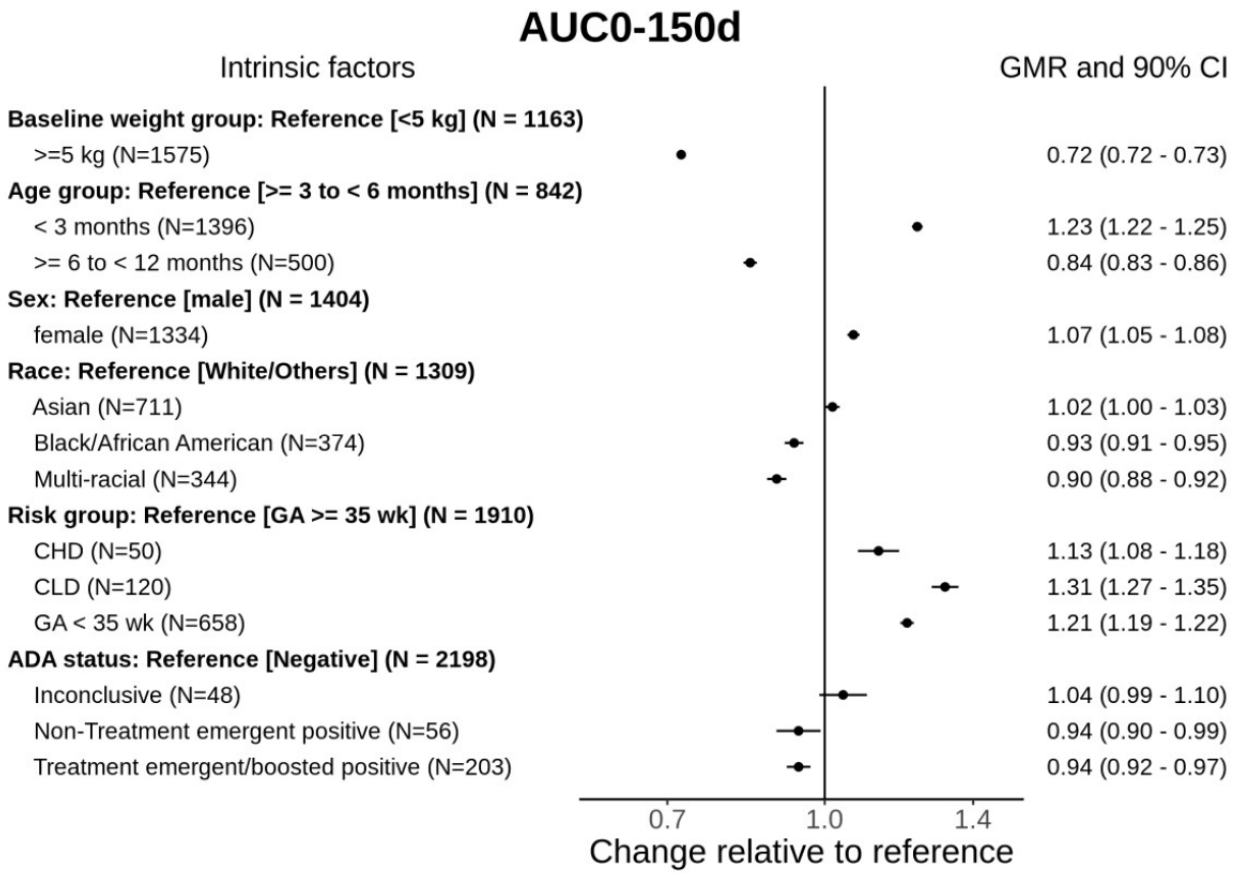
The variability of clesrovimab PK is considered low to moderate.

The Final Model Parameter Estimates for Clesrovimab PK in Infants indicate inter-individual variability (IIV) for Ka: 23.5% [95% CI 20.8-25.9], Vc/F: 8.12% [95% CI 7.18-8.97], and CL/F: 14.4% [95% CI 13.6-15.1].

Special populations

A forest plot of AUC0-150d is presented in Figure 14, along with corresponding GMR values. Similar results were obtained for Cmax (not shown in this report).

Figure 11. Forest Plot of EBE-based AUC0-150d for 105 mg Clesrovimab in Season 1



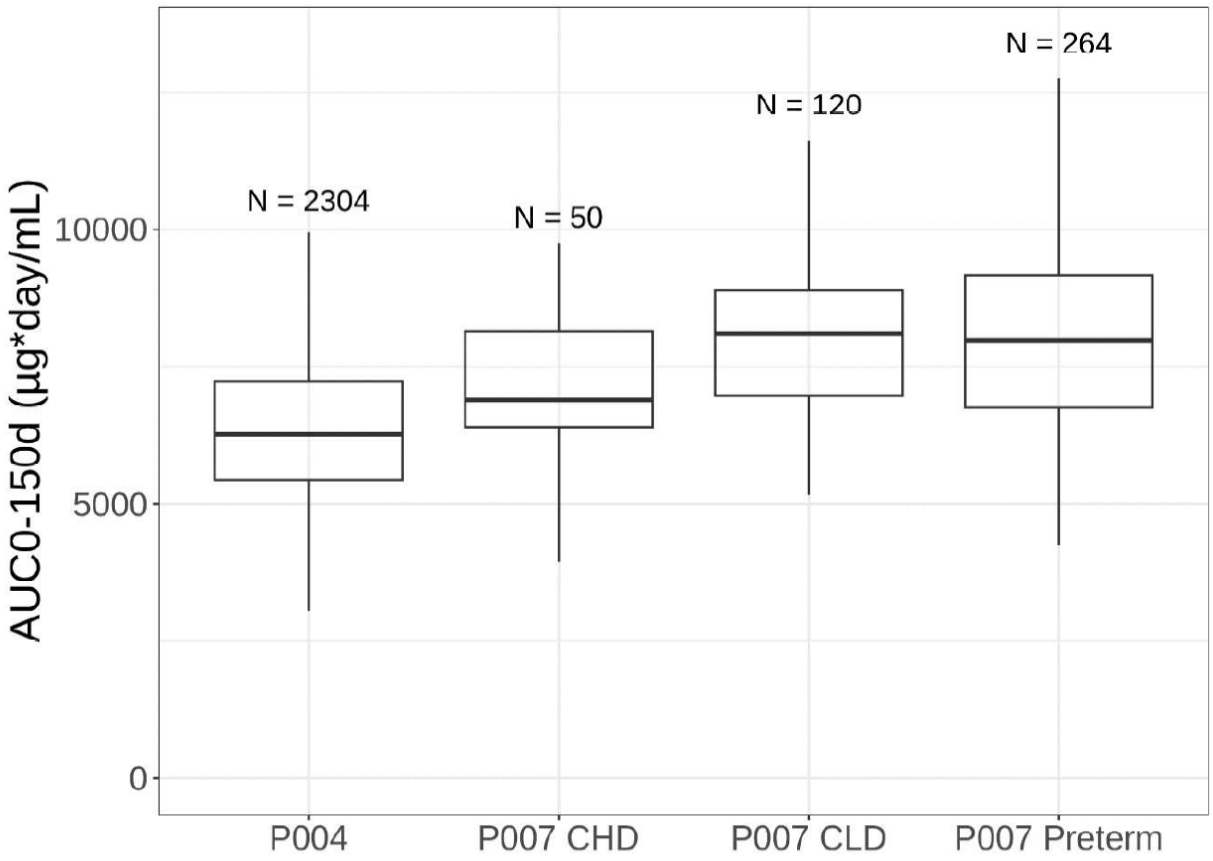
Source: forest-ebe-AUC150-20240917.png, ctd-plots-20240917-cert-hh.Rmd

Abbreviations: ADA=Anti-drug antibody; AUC0-150d = area under the concentration-time curve over first 150 days; CHD = Congenital Heart Disease; CI = confidence interval; CLD = Chronic lung disease; GMR = geometric mean ratio, N = sample size

The efficacy of clesrovimab was extrapolated from the healthy preterm and full-term infants in P004 to infants in P007 (at Increased Risk for Severe RSV Disease, including CHD, CLD and preterm infants) via PK bridging. The final infant PK model was used to generate individual (EBE-based) exposure measures of clesrovimab by season (e.g., AUCs, concentration at time of interest), for each participant enrolled in P004 and P007 and for which individual PK parameters were available. AUC0-150 was chosen as the PK parameter for extrapolation of efficacy from P004 to P007 because it was the primary exposure metric used for exposure-response analysis.

Estimates of AUC0-150 for all risk groups in P007 were comparable to or higher than the estimates observed in P004 (Figure 16). Similar trends are observed for C150 (not shown).

Figure 12. Comparison of AUC0-150d for Infants in P004 versus Risk Subgroups in P007 Season 1 Based on PopPK Analysis

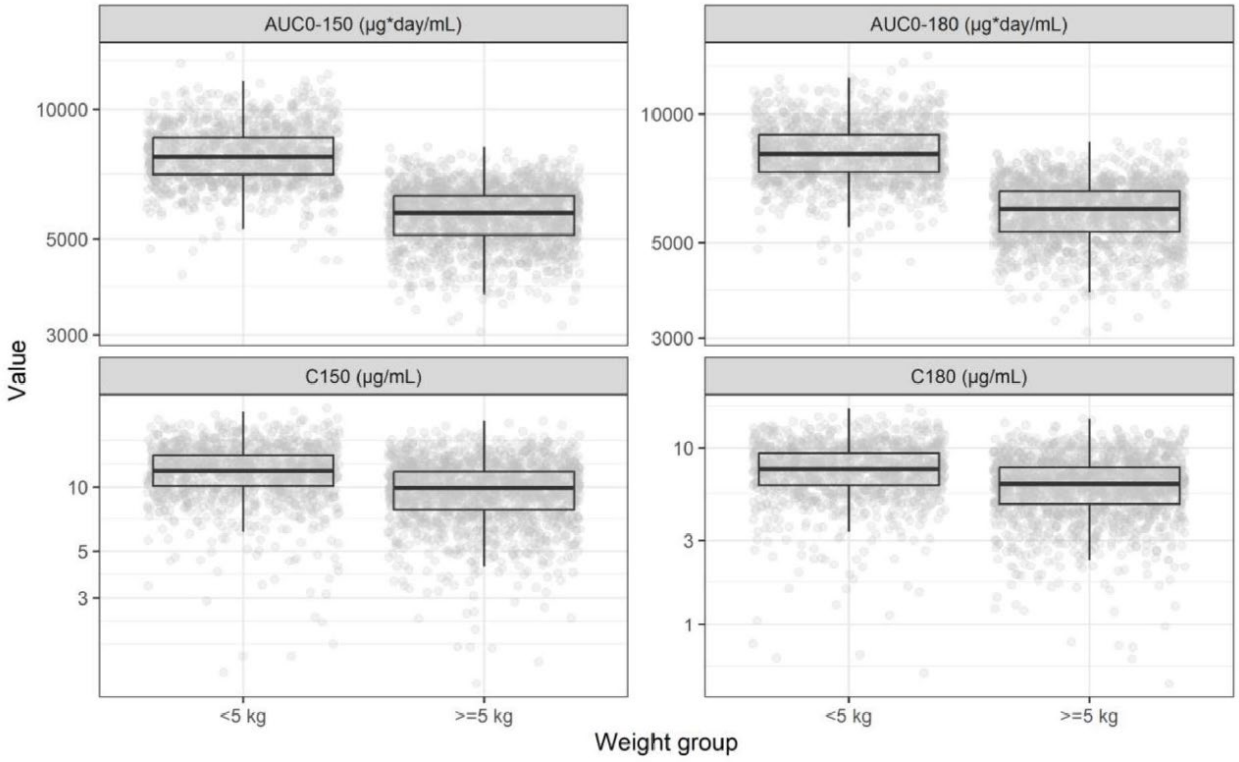


Source: parms-boxplot-auc150-s1-riskgroup-20240917.png, ctd-plots-20240917-cert-hh.Rmd

Abbreviations: AUC=area under the curve; CHD=congenital heart disease; CLD=chronic lung disease

EBE-based AUC0-150d for 105 mg Clesrovimab in Season 1 showed lower exposure of clesrovimab in ≥5kg patients compared to <5kg patients.

Figure 13. Box Plot of EBE-based Exposures for Clesrovimab in Season 1 Stratified by Body Weight



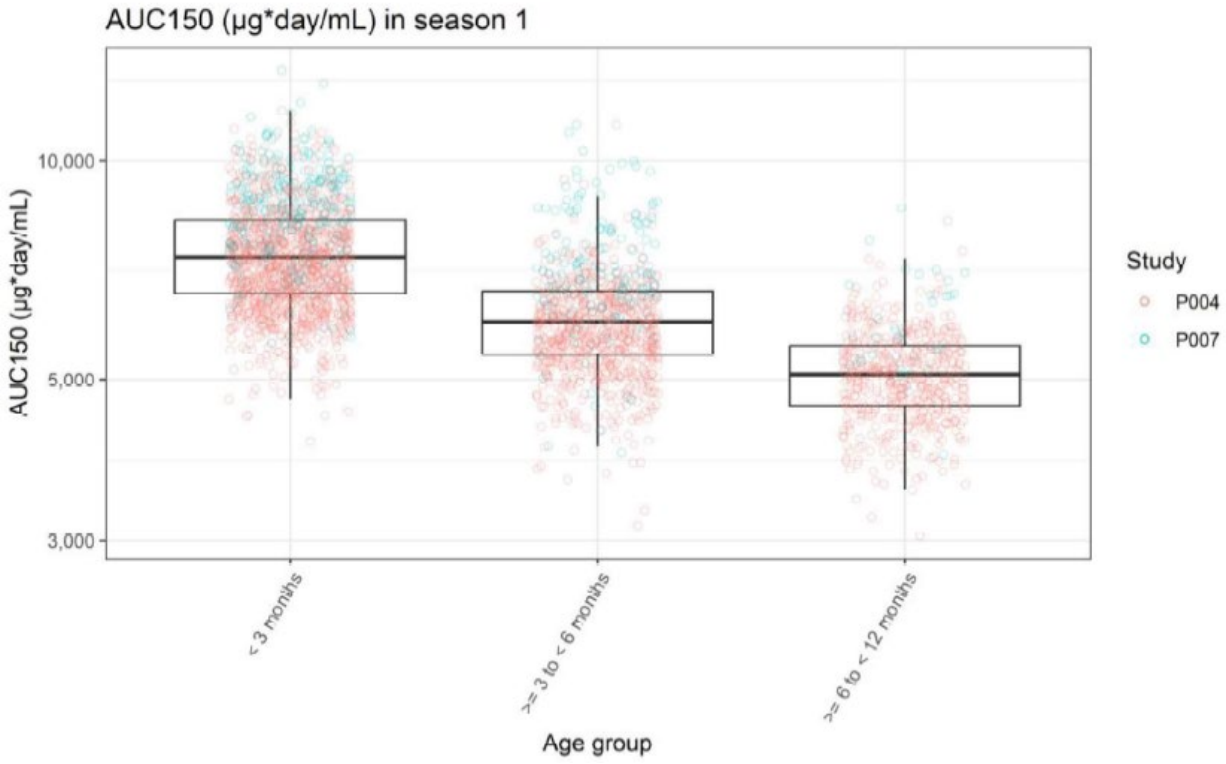
Source: 20240814-posthoc-popsim-expand-v21.html

Abbreviations: AUC150 = area under the concentration-time curve up to day 150 after dosing; AUC180 = area under the concentration-time curve up to day 180 after dosing; C150 = concentration on day 150 after dosing; C180 = concentration on day 180 after dosing

The estimated geometric mean AUC0-150d for infants with a baseline weight of 0.5 to 1.1 kg was 13,752 µg*day/mL, which is 113% higher than the overall geometric mean AUC0-150d (6470 µg*day/mL) observed in MK-1654-004 and MK-1654-007 in RSV Season 1.

Across all 2942 paediatric participants included in the analysis, the median (range) age was 3.02 months (0.07 to 12.0 months). Maturation (a function of age) was identified as a covariate on CL/F, where younger infants exhibited a lower clesrovimab clearance compared to older infants. This finding is consistent with other mAbs studied in an infant population and may be attributed to a higher FcRn capacity in younger children (Hardiansyah et al, 2018). The AUC0-150d 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 (Figure 14).

Figure 14. Boxplots Showing Relationship Between Age and Exposure Parameters



Pharmacokinetic interaction studies

Clesrovimab has no endogenous target and is therefore not expected to illicit DDIs via proinflammatory cytokine pathways or modifications of physiological processes. As such, extrinsic factors such as DDIs were not evaluated in this program.

2.6.2.2. Pharmacodynamics

Mechanism of action

Clesrovimab is a fully human IgG1 mAb with half-life extending YTE substitutions that binds to Site IV of the RSV F protein, thereby preventing viral/host cell fusion and neutralizing RSV.

Serum Neutralizing Antibodies (SNA) titer has been assessed throughout the clinical development program and is an indicator of the biologic activity of clesrovimab in humans after administration.

For more details see Non-Clinical Section.

PD Assay

For pharmacodynamic measurement, a validated commercially available kit was used. It was well described and setup correctly and considered valid for its intended use. The Applicant performed partial validations including accuracy and precision. Performance of the assays during clinical studies is acceptable.

RSV Neutralization Assay

A cell based RSV neutralization assay was developed to measure total neutralizing antibody levels to RSV strains A and B in human serum. Three generations of assays have been validated with respect to precision, dilutional linearity, specificity, and the upper and lower limits of quantitation. All measured parameters were acceptable.

RSV rapid antigen-based diagnostic kits

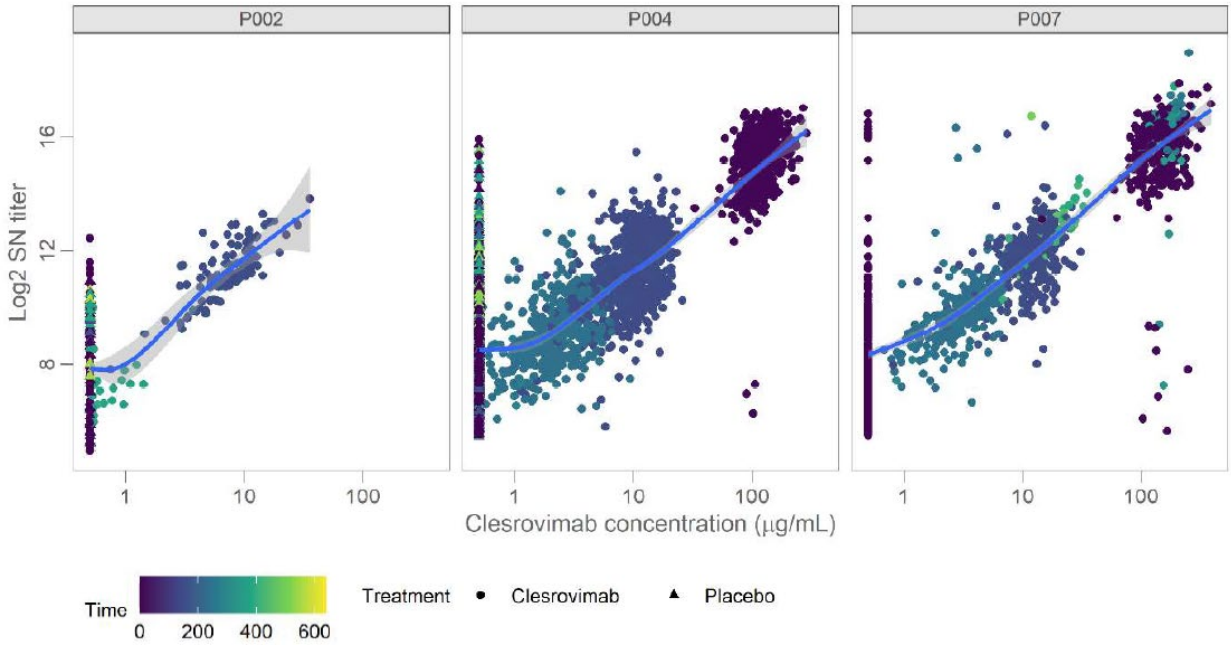
A separate study evaluating the impact of clesrovimab on RSV rapid antigen-based diagnostic assays was presented in Module 5 – 08P08S Virology Report. With the exception of one kit, no interference by clesrovimab (up to 5 µg/mL) was noted when the samples contained viral titers of $\geq 10^5$ PFU/mL. A recommendation is made to confirm negative results when clinical observations are consistent with RSV infection by an RT-PCR-based assay. This is reflected in the SmPC.

Primary and Secondary pharmacology

Consistent with the neutralizing mechanism of action of clesrovimab, SNA titers correlate with clesrovimab concentrations. In clinical studies, RSV SNA titers increased in a dose-dependent manner in adults who received clesrovimab IM and IV, and in infants who received clesrovimab IM. The relationship between clesrovimab concentrations and SNA titers was characterized using a linear PK/PD model. No covariates impacted the relationship between clesrovimab concentrations and RSV SNA titers (i.e. PK/SNA relationship).

The correlation between clesrovimab concentrations and log2 SN titer is presented in Figure Figure 15. Within each of the studies, SN titers increase with increasing clesrovimab concentrations. Also, SN titer observations of later time points seem to follow the same pattern as those obtained shortly after clesrovimab administration, indicating that a direct response relationship may be applicable.

Figure 15. Correlation Between Observed Clesrovimab Concentrations and Log2 SN Titers by Study



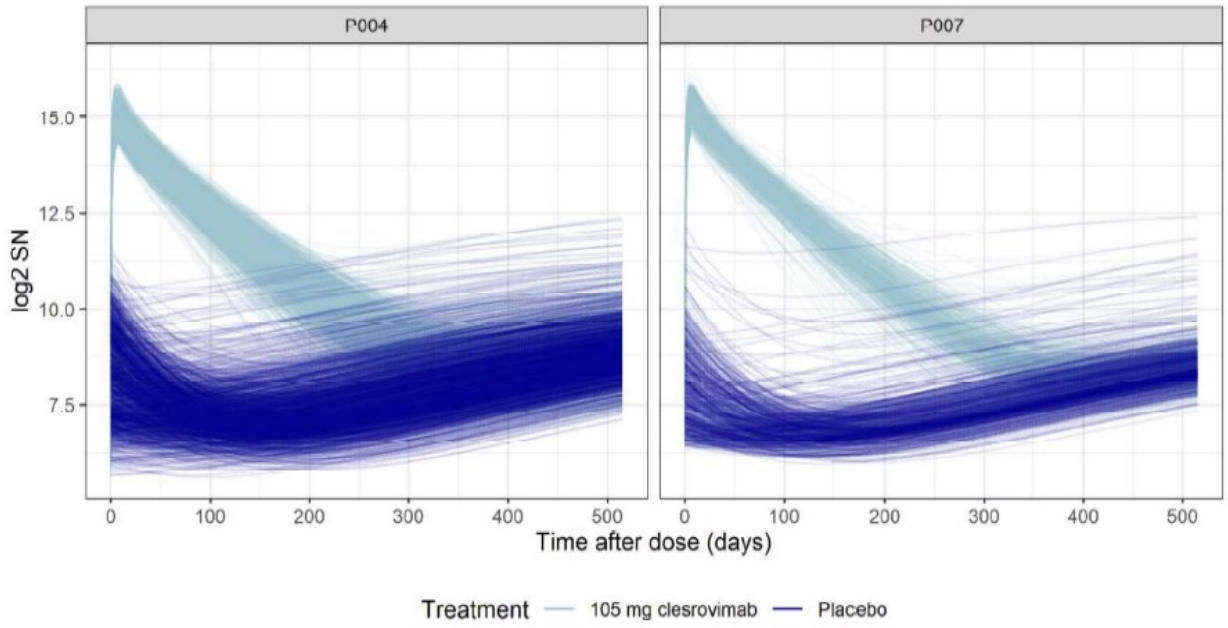
Notes: Based on subset of data for which for a given participant PK and SN observations were available at the same time point. Placebo and predose concentrations were set to 0.5 µg/mL for plotting purposes and are plotted as triangles. Solid line and shaded area correspond to LOESS smooth and

associated 95% confidence interval, and combines all data points (including predose and placebo) available per study.

Abbreviations: LOESS=locally weighted scatterplot smoothing; PK=pharmacokinetic; SN=serum neutralization

Simulations were performed for those 1757 infants in studies P004 and P007 that were included in the PK/PD final model and had received clesrovimab at any point in time. Individual EBE-based SN titer profiles after both clesrovimab or placebo administration simulated for this population are presented in Figure 16.

Figure 16. EBE-Based SN Titer Predictions for Participants in Studies P004 and P007



Notes: Simulations were performed for every infant that had EBE estimates for both PK and PD. The same infant was simulated twice: once after 105 mg clesrovimab administration, and once after placebo administration.

Abbreviations: SN=serum neutralization

Based on the PK/SNA model, the typical log2 SNA titer for a typical 5-kg full-term infant is predicted to be 8.74 at baseline, 11.5 at 4 hours (approximately 7-fold increase compared to baseline) following IM administration with a maximum log2 SNA titer of 15.0 at approximately 7 days (approximately 78-fold increase compared to baseline).

No dedicated secondary pharmacology studies have been performed with clesrovimab.

Data from adults who received increasing doses of clesrovimab indicated that there was no clinically meaningful effect of clesrovimab on the QTc interval. No dedicated ECG measurements were conducted in the infant population.

Immunological events

In MK-1654-002, the proportion of infants with ADA to clesrovimab was 13.1% at Day 150, 22.8% through Day 365, and 36.7% through Day 545. In 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 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; in RSV Season 2,

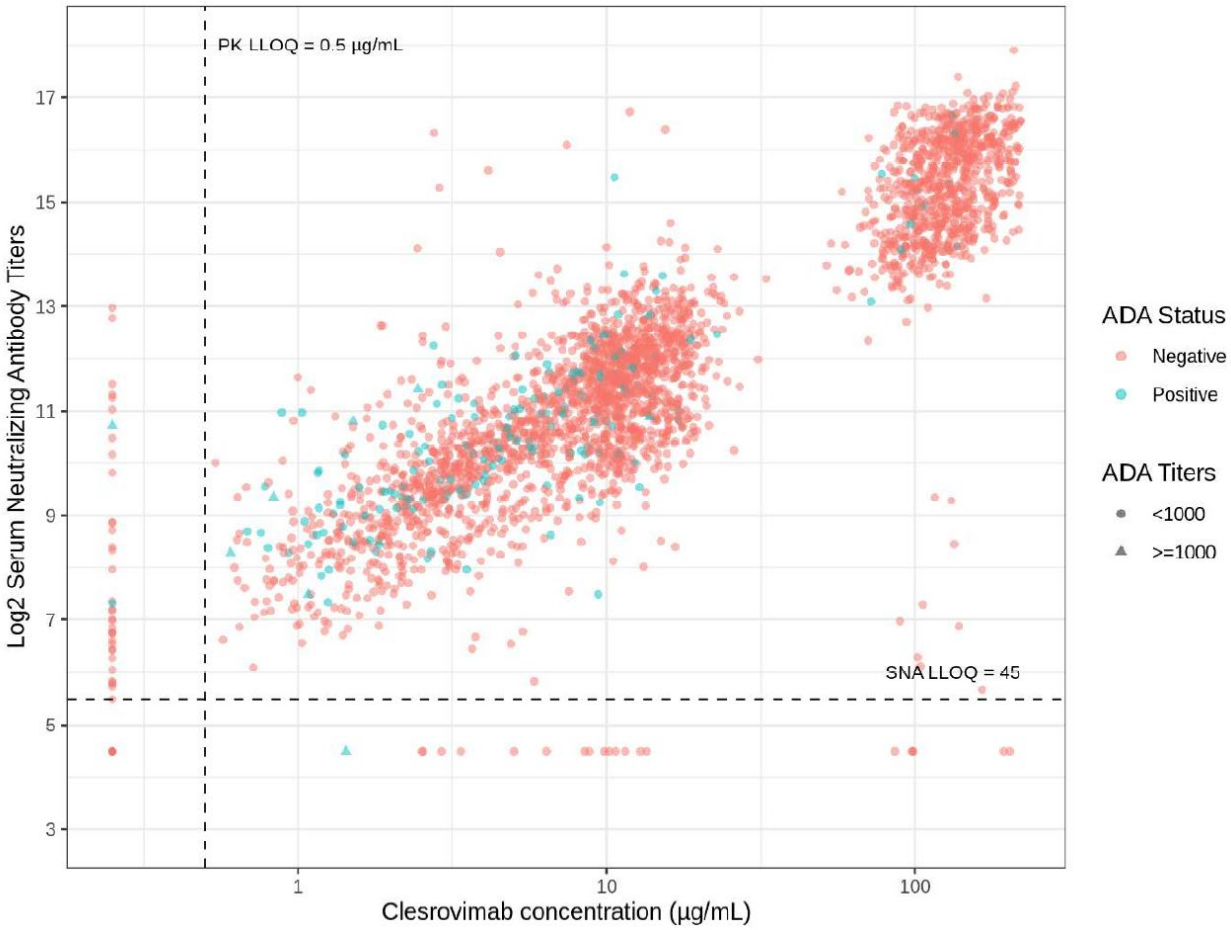
where an IM dose of 210 mg of clesrovimab was administered, the proportion of participants with positive ADA to clesrovimab was 1.0% at Day 7 and 7.7% at Day 150.

ADA status was not a significant covariate of clesrovimab PK in the paediatric popPK model. Compared to the ADA negative reference group, participants with treatment-emergent/treatment boosted ADA had 6% lower exposure. Participants with non-treatment emergent ADA also had 6% lower exposure compared to the ADA negative group.

The relationship between PK, SNA, and ADA was evaluated to explore a potential neutralizing effect of ADA on clesrovimab. This evaluation was used in lieu of a standalone NAb assay. Data from MK-1654-004 and MK-1654-007 indicate a clear relationship between increasing clesrovimab concentration and SNA titer through Day 240 for both ADA positive and ADA negative subjects (Figure 10-8). For a given clesrovimab concentration, SNA titers in ADA positive samples generally overlapped with those from ADA negative samples. No systematic trend between ADA positivity and reduced SNA titer was identified, indicating that ADA generally did not neutralize the activity of clesrovimab. This finding is further supported by model-predicted SNA titer-time profiles, which showed a similar level of SNA titer in ADA positive participants, compared to those who were ADA negative (Figure 18).

An exploratory plot for the PK-SNA relationship stratified by ADA status is presented in Figure 17.

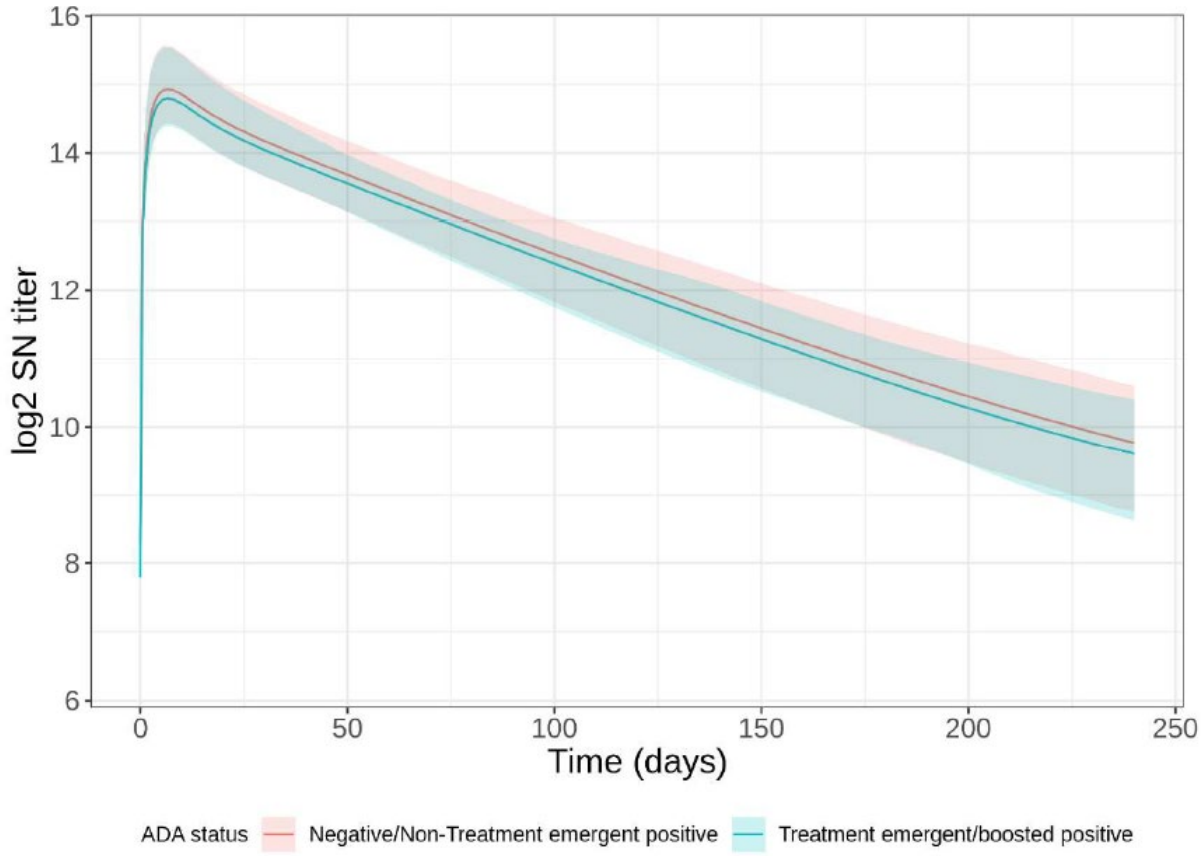
Figure 17. Observed PK-SNA relationship by ADA status in P004 and P007, Season 1



Notes: ADA status was not assessed at each sampling time point. LOCF was applied for ADA status in case actual ADA status was not available for a given time point.

Abbreviations: PK = Pharmacokinetics; ADA=Anti-drug antibody; SN=serum neutralization; LLOQ = Lower limit of quantification; LOCF = Last observation carried forward

Figure 18. Simulated SNA titers by ADA status



Source: sn-sim-p004-ada-20240917.png, ctd-plots-20240917-cert-hh.Rmd
Notes: Solid line and shaded area represent median and 5th-95th percentile interval
Abbreviations: ADA=Anti-drug antibody; SN=serum neutralization

Exposure-response analysis

The objectives of the exposure-efficacy analysis based on clinical data from Study MK-1654-004 were to characterize the relationship between clesrovimab exposure and efficacy endpoints. Exposure-efficacy explorations were conducted for all efficacy endpoints. Exposure-efficacy relationships were formally evaluated for 6 endpoints: RSV-MALRI (Days 1 to 150), RSV-A-MALRI (Days 1 to 150), RSV-B-MALRI (Days 1 to 150), RSVMALRI (Days 1 to 180), RSV-hospitalization (Days 1 to 150), and RSV-2 indicators of LRI/severity (Days 1 to 150).

For efficacy endpoints, only the first occurrence of each endpoint was considered in this analysis. A modified Poisson regression model with robust variance (to mitigate overestimation of the estimated relative risk when analyzing binomial data) was applied to estimate the relative risk of these events as a function of clesrovimab exposure. For this analysis the response variable for each efficacy endpoint is defined as whether a participant has experienced an event. AUC0-t, where 0-t is either days 1 to 150 or days 1 to 180 to match the efficacy endpoint being evaluated, was used as a starting point for the exposure metric used to drive the exposure-efficacy model. For sensitivity analysis with placebo data, exposure was imputed as 0 for participants receiving placebo.

Table 4. Data disposition table for participants in the analysis dataset

	Placebo	**MK-1654 105 nmg IM**		**Total**
		With EBE from popPK analysis	Without EBE from popPK analysis	
N (%)	1200 (33.3%)	2291 (63.7%)	108 (3.0%)	3599

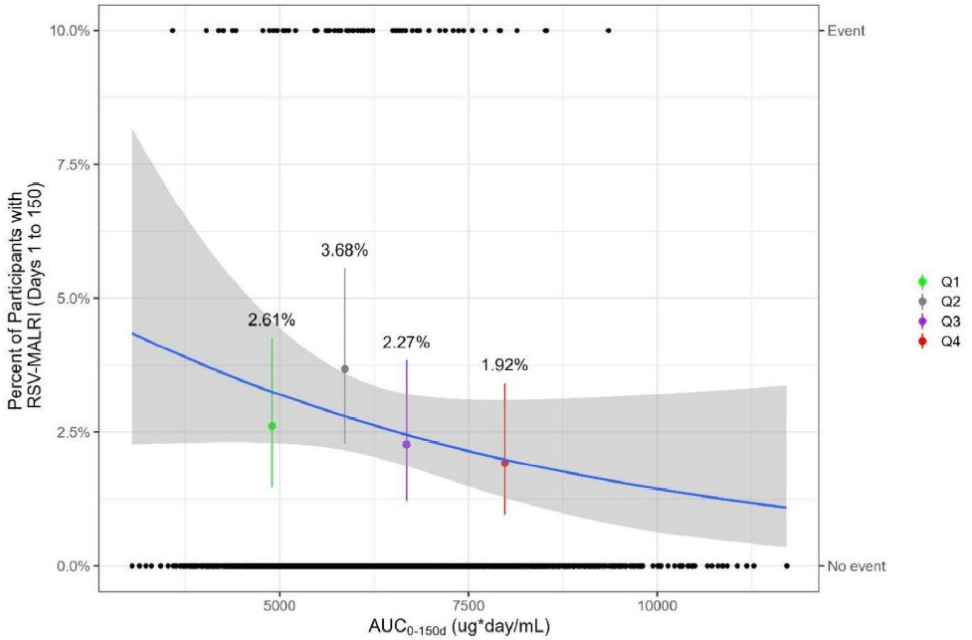
PK = pharmacometrics; popPK = population pharmacometrics; N = number of participants.

Individual exposures (AUC0-150d and AUC0-180d) were derived based on the empirical Bayesian estimates from the popPK analysis for participants in study MK-1654-004. Summary statistics for the exposure quartiles are presented in Table 5.

Table 5. Number (%) of participants with efficacy events for all endpoints by AUC0-150d Quartiles

Endpoints Metrics	**Q1**	**Q2**	**Q3**	**Q4**
RSV-MALRI D1-150	2.61% (15/575)	3.68% (21/571)	2.27% (13/573)	1.92% (11/572)
RSV-Hospitalization D1-150	0.35% (2/575)	0.35% (2/571)	0.52% (3/573)	0.35% (2/572)
RSV Severe MALRI D1-150	0% (0/575)	0.18% (1/571)	0% (0/573)	0.17% (1/572)
RSV-MALRI 2 Indicators of severity D1-150	0.17% (1/575)	0.53% (3/571)	0.35% (2/573)	0.7% (4/572)
MALRI due to any cause	26.26% (151/575)	20.67% (118/571)	21.64% (124/573)	20.1% (115/572)
RSV-LRI Hospitalization D1-150	0% (0/575)	0.35% (2/571)	0.17% (1/573)	0.35% (2/572)
LRI Hospitalization due to any cause D1-150	1.39% (8/575)	1.93% (11/571)	2.79% (16/573)	4.2% (24/572)
Non-RSV Hospitalization D1-150	24.7% (142/575)	18.21% (104/571)	19.37% (111/573)	18.18% (104/572)
RSV-MALRI excluding other pathogens D1-150	0.87% (5/575)	2.45% (14/571)	1.75% (10/573)	1.57% (9/572)
RSV-ARI D1-150	7.3% (42/575)	8.93% (51/571)	5.58% (32/573)	3.5% (20/572)
RSV-MALRI including PCR results D1-D150	2.61% (15/575)	3.68% (21/571)	2.44% (14/573)	2.1% (12/572)
RSV-Hospitalization including PCR results D1-150	0.35% (2/575)	0.35% (2/571)	0.52% (3/573)	0.52% (3/572)

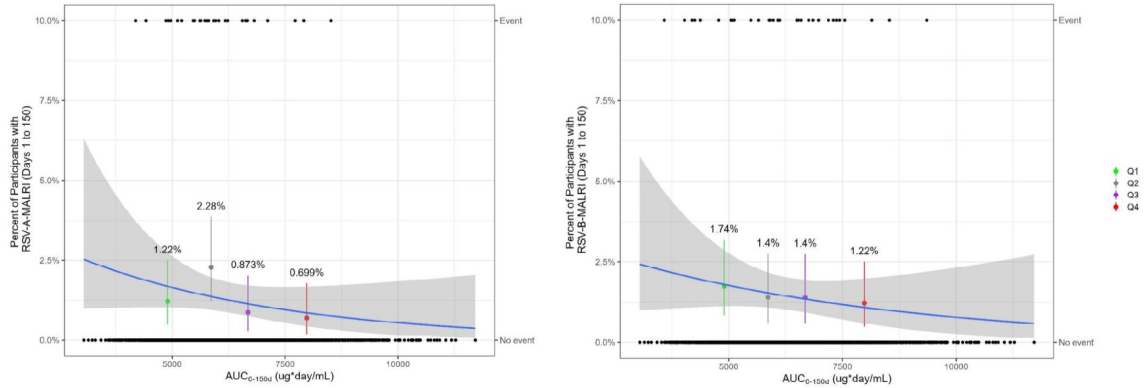
Figure 19. Observed proportion and predicted probability of event of RSV-MALRI (Days 1 to 150) versus AUC0-150d



AUC0-150d= area under the curve from day 1 to day 150; CI = confidence interval

Black dots indicate data from individual participants. Closed circles (error bars) show the observed proportion of participants with event (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile. Solid (blue line and gray area) curves show the model-predicted (logistic regression) probability of the event (95% CI). Median (range) AUC0-150d (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.

Figure 20 and Figure 21 Observed proportion and predicted probability of event of RSV-A MALRI (Day 1 to 150), and RSV-B MALRI (Day 1 to 150), respectively, versus AUC0-150d

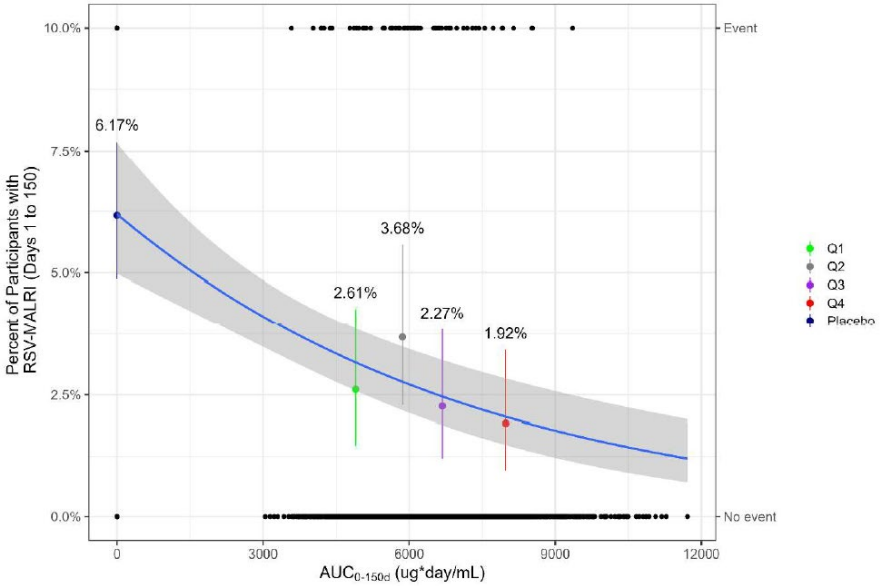


AUC0-150d= area under the curve from day 1 to day 150; CI = confidence interval

Black dots indicate data from individual participants. Closed circles (error bars) show the observed proportion of participants with event (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile. Solid (blue line and gray area) curves show the model-predicted (logistic regression) probability of the event (95% CI). Median (range) AUC0-150d (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.

Exposure-response with placebo participants was performed as sensitivity analysis and is presented in Figure 22.

Figure 22. Observed proportion (participants in the treatment group with evaluable PK concentration and participants in the placebo group) predicted probability of event of RSV-MALRI (Days 1 to 150) versus AUC0-150d



The estimated parameters using logistic model and modified Poisson model were provided. The statistically significant relationship between AUC0-150d and response of RSV-MALRI (Days 1 to 150) (with placebo) is due to the higher proportion of events in placebo participants.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

The presented assays for determination of MK-1654 in human serum, RSV A or RSV B in nasopharyngeal swabs, were well described and established. Analytical procedures for the measurement of neutralizing antibodies against RSV A were validated. Only RSV A was tested during clinical studies, as clesrovimab demonstrated equipotency against both RSV A and RSV B strains. This is acceptable.

For nasopharyngeal swabs, clinical observations consistent with RSV infection, despite negative results in rapid antigen-based diagnostic kits are recommended to be confirmed by RT-PCR-based assay.

The ECL assay to detect anti-MK-1654 (anti-clesrovimab) antibodies in human serum was set up correctly and is considered state of the art. The assay is considered valid for its intended use. No standalone Nab assay has been developed. However, the presented approach to conclude that ADA do not have neutralizing effect on clesrovimab activity is found acceptable.

Evaluation and qualification of models

The goal of a priori developing an adult PopPK model was to support subsequent PK and PK/PD model development for preterm and full-term infants from birth through their first or second RSV season, who are the target population for clesrovimab treatment.

The paediatric PopPK analysis was based on 5850 samples from 2942 participants. As a starting point, a preliminary infant PopPK model was developed using available PK data from preterm and full-term

infants in study MK-1654-002. The final infant PopPK model had a 2-compartmental structure and included linear absorption and elimination pathways. BW was included as an allometric scaling factor on CL, Vc, and Ka, with estimates normalized on a BW of 5 kg. Informative priors for selected PK parameters were based on estimates for healthy adults from a preliminary PopPK analysis. After including additional data provided from studies MK-1654-004 and MK-1654-007, ultimately, prior information from the adult model was used for Ka and Vp. To account for rapid growth in infants, the base model included allometric scaling effects (centered on a reference body weight of 5 kg) on clearance and volume parameters, using time-varying body weight. In addition, a maturation function on CL based on postnatal age and gestational age was included, similar to what was reported for palivizumab (Robbie et al, 2012) and nirsevimab (EPAR Beyfortus). As the rate of absorption is different between palivizumab and nirsevimab, a sensitivity analysis was conducted to evaluate goodness of model fit with differing values of Ka for clesrovimab. Additional covariates included sex, race, ethnicity, CHD, CLD, gestational age, adjusted age (postnatal age + gestational age – 40 weeks), and time-varying ADA. IIV was assumed to be log-normally distributed and was included on CL, Vc, and Ka. Eta-shrinkage of IIV Ka, IIV Vc/F, and IIV CL/F were 74.6%, 71.9%, and 12.3%, respectively. Epsilon-shrinkage of the proportional + additive error model was 26.6% for both epsilons. Due to the high shrinkage of IIV estimates for Ka and Vc, graphical evaluation was limited to IIV on CL. In addition to body weight and maturation function, the final model contained an effect of race on CL. Model parameter estimates did not change notably between the base and the final model.

The PK/PD analysis was based on 8458 samples from 2620 participants when using the M3 method (maximizing the likelihood for the data above the limit of quantification (LOQ) and treating BQL data as censored), and 7248 samples from 2531 participants when using the M1 method (discarding BQL observations). The overall performance was described best for M3 (Ahn et al, 2008).

An integrated paediatric PK/PD modelling analysis was performed to characterize the relationship between clesrovimab PK and RSV SNA titers in infant participants from MK-1654-002, MK-1654-004, and MK-1654-007 studies. In accordance with natural SNA titer time-course in infants described in literature (initial SNA titers comparable to SNA titers in adults due to placental transfer in full-term infants declining after birth, with a rebound after approximately 6 months of age), the model also included an exponential decline function on SN baseline titer as a function of postnatal age and an effect of gestational age on parameter base. The Applicant retained the effect of gestational age on base despite lack of IIV reduction, given its physiological plausibility. EBEs obtained from the final infant PopPK model was used as input in the PK/PD model. Outliers were excluded in the final model. IIV baseline and IIV matur had eta-shrinkage of 54.9% and 55.3%, respectively. Epsilon-shrinkage was 7.6%. A stepwise covariate analysis was performed using the developed base model. This analysis showed that covariates including CHD, CLD, gestational age, postnatal age, adjusted age, and time varying ADA, did not affect the PK/SNA relationship. The final paediatric PK/PD model structure describing the relationship between clesrovimab concentrations and RSV SNA titers was similar to the adult model structure, using a linear direct response relationship, with a dynamically changing SN baseline and additive residual error on log2 titer scale.

Pharmacokinetics

Process 1 formulation was used in studies P001, P002 and P003, whereas Process 2 formulation was used in the pivotal safety and efficacy studies P004 and P007. It is agreed that Process 1 and 2 show similar PK in infants (P002 NCA vs POPPK modelling using all infant data).

Absorption of the IM formulation was appropriately characterized with an estimated Ka of approximately 0.286 day-1 (23.5% CV), and a median Tmax of 6.5 (range 4.7, 11.0) days, as indicated in Section 5.2 of the SmPC. IV administration was not studies in infants. Therefore, the estimated bioavailability was derived from the adult population and is estimated to be approximately

77.8% after IM administration to the thigh, which is higher as compared to IM administration to the arm. It can be assumed that bioavailability is comparable in infants. The total volume of distribution (Vc+Vp) of clesrovimab, adjusted for bioavailability, is with 646 mL higher than the expected blood volume for a typical infant of 5 kg (375-400 mL), which indicates that clesrovimab may distribute into tissues. The apparent clearance (CL/F) of clesrovimab was estimated at approximately 19.7 mL/day (0.82 mL/h or 0.164 mL/h/kg) for a reference 5-kg infant. The estimated t½ for human IgG is approximately 20 days. By adding the YTE amino acid substitution to the Fc portion of the antibody the terminal half-life was extended to 44.0 days (13.4% GCV) for infants. The expected consequence of metabolism of biological products is degradation to small peptides and amino acids, which is independent of hepatic enzymes.

In preterm infants, PK of clesrovimab was dose-proportional following administration of single IM doses of 20 mg to 210 mg and after intravenous administration in adults (300-3000 mg). Full-term infants had approximately 20% lower exposures (Cmax and AUC0-inf) than preterm infants at the 100 mg IM dose, which is likely attributed to body weight and age differences. Interindividual variability is considered low to moderate with 23.5%, 8.12% and 14.4% for Ka, Vc/F and CL/F, respectively. However, spaghetti plots reveal that in rare cases, patients experienced increased clearance. In one instance this could be ascribed to positivity for ADA with a high titer (3000 mg IV), whereas in another instance (1000 mg IV), the ADA analysis fell out negative.

The posology of clesrovimab is 105 mg in season 1 and 210 mg in season 2 independent of body weight, gestational age and co-morbidities. Higher doses than 210 mg in infants have not been administered. According to POPPK simulations, the exposure is similar after 105 mg in season 1 and 210 mg in season 2.

Special populations

The Applicant intends to extrapolate the efficacy of clesrovimab from the healthy preterm and full-term infants in study MK-1654-004 to infants in study MK-1654-007 (at Increased Risk for Severe RSV Disease, including CHD, CLD and preterm infants) via PK bridging. PK estimates for infants at increased risk of severe RSV disease included in MK-1654-007 generally showed higher exposures compared to full-term infants studied in MK-1654-004. Since the exposure-response relationship is relatively flat, and no safety risks are apparent following the observed higher exposure in infants at increased risk for severe RSV disease, an adjustment of the dose in those infants is not considered necessary.

Minor differences in exposure were observed for females (90% CI for AUC0-150d: 1.05-1.08) compared to males, and Asian (1.00-1.03), Black/African American (0.91-0.95) and Multi-racial (0.88-0.92) patients compared to White/Others. These differences are considered unlikely to impact the efficacy due to lower exposure or safety due to higher exposure.

Considerably lower exposure was observed in infants weighing ≥5kg compared to <5kg (90% CI 0.72-0.73). Currently, a flat dose of 105 mg for all infants, irrespective of body weight is foreseen, in contrast to another RSV mAb, which is used at double dosing in infants weighing ≥5kg (Beyfortus SmPC). As the exposure-response relationship is relatively flat, and as efficacy is not substantially different between the subgroups (≥5kg vs <5kg), no weight-based dosing is considered necessary. However, no infants below 1.1kg were dosed in the clinical programme. The estimated geometric mean AUC0-150d for infants with a baseline weight of 0.5 to 1.1 kg was 113% higher than the overall geometric mean AUC0-150d.

Age was identified as a covariate on CL/F, where younger infants exhibited a lower clearance compared to older infants. Lower clearance in younger infants is consistent with other mAbs studied in an infant population and may be attributed to a higher FcRn capacity in younger children (Hardiansyah et al,

2018). In absolute terms, the median clesrovimab concentration (AUC150) was lowest in the subgroup of >6 months of age (compared to any other subgroup stratified by risk or weight). Although efficacy estimates for some endpoints were lower in older and heavier infants, 95% CI widely overlapped. In addition, estimates obtained across additional efficacy endpoints are consistent with trends from the overall population. No exposure threshold required to confer protection against RSV is known, which was reflected in 5.2 of the SmPC upon request.

Clesrovimab is currently proposed to be administered as a single dose (except after surgery, where a second dose is foreseen). Hence, the risk for accumulation is considered negligible. The highest exposure was observed for infants with lower body weight, preterm infants and infants with CHD/CLD. Thus, those infants are at highest risk of experiencing adverse drug reactions.

No infants with renal or hepatic impairment were included in the studies and no effort was made to investigate the effect of renal or hepatic impairment on the pharmacokinetics of clesrovimab. As the clearance of clesrovimab is not expected to be via renal or hepatic clearance mechanisms, this is acceptable. The wording in section 5.2 of the SmPC regarding renal and hepatic impairment is acceptable.

Pharmacodynamics

Clesrovimab is a fully human immunoglobulin G1 kappa (IgG1κ) neutralising monoclonal antibody with a triple amino acid substitution (YTE) in the Fc region which increases binding to the neonatal Fc receptor leading to an extended serum half-life. Clesrovimab has no endogenous target. Clesrovimab provides passive immunity by targeting the RSV outer membrane fusion (F) protein to prevent viral entry into cells. Clesrovimab targets a conserved epitope on antigenic site IV on the fusion F protein and binds to RSV pre-fusion F glycoprotein and post-fusion F glycoprotein with equilibrium dissociation constant values (KD) of 71 pM and 480 pM, respectively. RSV A and B isolates are expected to be equipotently neutralized by clesrovimab, based on similar in vitro IC50 values for both subtypes, and assumed similar KDs based on highly conserved binding epitopes. The expected absence of Fc effector function was included in Section 5.1 of the SmPC upon request.

The primary pharmacodynamic effect of clesrovimab is demonstrated by serum neutralizing antibodies (SNA). SNA titers correlate with clesrovimab concentrations, irrespective of the time point after clesrovimab administration. Hence, a linear PK/PD model was used, which is considered appropriate. No covariates impacted the relationship between clesrovimab concentrations and RSV SNA titers. Based on the PK/SNA model, the maximum log2 SNA titer for a typical 5-kg full-term infant is predicted to be approximately 78-fold increase compared to baseline at approximately 7 days after administration. However, no SNA titer threshold to confer efficacy is known for clesrovimab. The duration of protection offered by a single dose of clesrovimab could extend through 6 months, but the observation is limited by a low event incidence that occurred after 5 months postdose.

No thorough QTc study was performed, since clesrovimab is not expected to interfere with the hERG channel. Routine ECG was performed in adults in the phase 1 trials with no observed meaningful changes in the QTc interval. ECG was not measured in infants which is acceptable.

Clesrovimab may be given concomitantly with childhood vaccines, and interference with the active immune response to those is not expected.

Immunogenicity is a minor concern, if the product is intended for one time administration only. In MK-1654-004 and MK-1654-007, 12.0% (124/1033) and 13.0% (34/261) of participants who received clesrovimab were ADA-positive through Day 240 of Season 1, respectively. Participants with ADA had 6% lower exposure, and ADA status was not found a significant covariate of clesrovimab PK. It is agreed that this difference in exposure is likely clinically irrelevant for the first season. Regarding efficacy there was a slight discrepancy in the results as to whether ADA could compromise the effect of

clesrovimab in study MK-1654-004. Reassuringly, no systematic trend between ADA positivity and reduced SNA titer was identified. Beyond Day 240, the incidence of ADA increased up to 58.6% through Day 515 in study MK-1654-004. In the event that a 2nd administration will be claimed in the label, the effect of repeated dosing or ADA on pharmacology should be investigated.

Exposure-Response

The proportion of efficacy events was low and comparable across all AUC0-t quartiles and for both observation periods investigated (150d and 180d) following a single 105 mg IM dose of clesrovimab. In total, data indicate that exposure-efficacy relationship is relatively flat in the exposure range associated with a single 105 mg IM dose of clesrovimab in Season 1. The applied logistic and modified Poisson models indicated that significant relationships between the probability of event and corresponding exposure metrics were all due to the higher proportion of events in the placebo arm. However, the assumed duration of protection of 6 months is solely based on efficacy data, and the observation is limited by a low event incidence that occurred after 5 months postdose.

2.6.4. Conclusions on clinical pharmacology

Preterm and full-term infants from birth through their first RSV season are the target population for clesrovimab treatment. Based on adult and sparse paediatric PK samples, PopPK and PK/PD models were developed, which adequately described the pharmacology in the target population.

Efficacy data in infants at increased risk for severe RSV disease (CHD, CLD and preterm infants) is limited, as study MK-1654-007 is not powered to formally evaluate efficacy. Hence, efficacy of clesrovimab in high-risk infants is intended to be extrapolated via PK bridging. PK estimates for high-risk infants generally showed higher exposures compared to full-term infants. Since the exposure-response relationship is relatively flat, and no safety risks are apparent following the observed higher exposure in high-risk infants, the CHMP is of the opinion that an adjustment of the dose is not considered necessary. Considerably lower exposure was observed in the subgroup of infants >6 months of age, but estimates obtained across several efficacy endpoints are consistent with trends from the overall population.

SNA titers correlate with clesrovimab concentrations and no systematic trend between ADA positivity and reduced SNA titer was identified.

2.6.5. Clinical efficacy

2.6.5.1. Dose-response studies

Study MK-1654-002:

This was a Phase 1b/2a, randomized, placebo-controlled, single ascending dose, multisite, global, double-blind study to evaluate the safety, tolerability, and PK study of clesrovimab in 181 healthy preterm and full-term infants. Infants with gestational age either ≥29 to 35 weeks (ie, preterm infants) or >35 weeks (ie, full-term infants), chronological age ≥2 weeks to 8 months, and weighing ≥2 kg at the time of screening were enrolled and randomized 4:1 within 1 of 5 panels to receive clesrovimab or placebo. The single-dose levels were 20, 50, 75, and 100 mg administered IM. No participant received more than 1 dose of clesrovimab. Therefore, a participant only took part in 1 panel of the study. Sampling of blood was performed for 365 days relative to the time of IM injection.

A popPK model was developed using the sparse PK samples to predict mean serum concentrations of clesrovimab and PK parameters, which are summarized in Section 2.6.2.1. Clesrovimab exposures increased in a manner that appeared approximately proportional to dose.

After dosing with MK-1654, RSV SNA titers appeared to increase in a dose dependent manner at Day 150 in preterm infants. The small sample size in the MK-1654 20 mg group did not allow for a meaningful comparison. RSV SNA titers in preterm and full-term infants were generally comparable for the 100 mg dose of MK-1654 at Day 150.

The incidence of RSV-associated LRI, RSV-associated hospitalization, and RSV-associated ARI was lower in infants in the combined MK-1654 dose groups (consisting of all MK-1654 groups across all panels) and MK-1654 100 mg dose groups (consisting of MK-1654 100 mg groups in Panels D and E) compared with infants in the placebo group. The CIs for efficacy for each of these endpoints were wide due to the small sample size and should be interpreted with caution.

Based on modelling of MK-1654-002 data, along with an MBMA (model-based meta-analysis), a 105-mg IM dose was selected for all healthy preterm and full-term infants born during or entering their first RSV season in MK-1654-004. Modelling results demonstrated that a 105-mg IM dose had a high likelihood of providing high efficacy for the prevention of RSV-associated MALRI in the first RSV season for all infants in MK-1654-004 (Table 6).

Table 6. Simulated RSV-MALRI Incidence Rates and Efficacies for Different MK-1654 Doses Using PK Model Run71

Dose (mg)	IR (%)	RSV-MALRI Efficacy [95% CI]	Pr(E>60%)	Pr(E>65%)	Pr(E>70%)
0	12.51	-	-	-	-
60	3.887	0.691 [0.580 - 0.772]	0.95	0.785	0.422
75	3.577	0.713 [0.601 - 0.794]	0.976	0.882	0.607
90	3.389	0.729 [0.615 - 0.809]	0.985	0.923	0.713
105	3.247	0.740 [0.624 - 0.820]	0.989	0.943	0.776

Abbreviations: E=Efficacy, IR=Incidence Rate, RSV=Respiratory Syncytial Virus, MALRI=Medically Attended Lower Respiratory Tract Infection, CI=Confidence Interval; Pr=Probability

Notes: Efficacy calculated as 1- IR(MK-1654)/ IR(pbo).

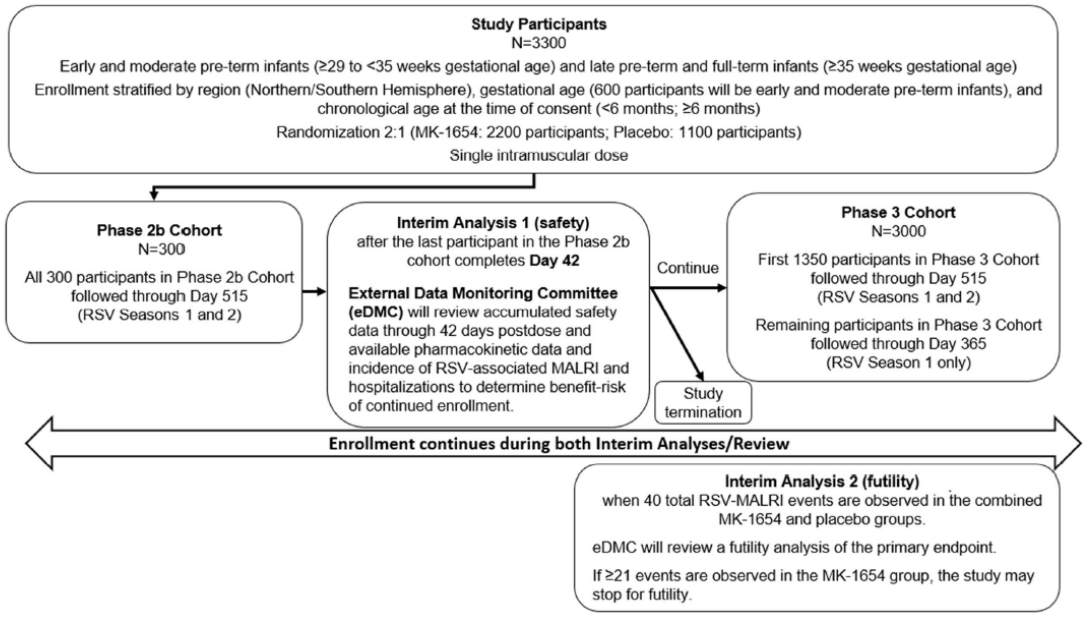
2.6.5.2. Main study(ies)

MK-1654-004: 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

Study code	MK-1654-004
EU CT number	2022-500350-42-00
NCT number	NCT04767373
ISRCT number	
Other identifier(s)	CTR20221857
Location in eCTD	5.3.5.1

Methods

Figure 23: Study schema MK-1654-004



Study assessments

At Visit 1, potential participants were evaluated to determine whether they met entry requirements. Potential participants were screened at the study site.

Surveillance for Respiratory Infection Symptoms

The purpose of this surveillance was to:

1) Identify if the following respiratory infection symptoms have occurred or worsened:

- Signs/symptoms of ARI and indicators of ARI severity (at least 2 of the following for at least 2 days):
  - Cough
  - Congestion (stuffy or runny nose)
  - Fever
  - Trouble feeding
- Signs/symptoms of LRI and indicators of LRI severity, as follows:
  - Cough or difficulty breathing for at least 1 day; AND
  - At least 1 of the following:
    - Wheezing
    - Chest wall in-drawing/Retractions
    - Tachypnea (rapid breathing)

If respiratory infection symptoms were reported (as defined above), the participant should have been assessed at the site by the investigator or medically qualified designee (see below "Respiratory infection assessment").

2) Identify if the participant was being assessed for respiratory infection symptoms in an outpatient or inpatient clinical setting (outpatient clinic, Emergency Department, urgent care center, or hospital), and if this was the case, the participant should have been assessed at the site by the investigator or medically qualified designee.

Requirements for Scheduling a Respiratory Infection Assessment

To identify potential cases of RSV-associated LRI, participants with any respiratory infection symptoms were assessed at the site by the investigator or medically qualified designee.

A respiratory infection assessment was required when:

- Respiratory infection symptoms were reported (see above).
- New respiratory infection symptoms arose or symptoms worsened during an existing episode.
- The participant was seen in an outpatient or inpatient clinical setting for respiratory infection symptoms.

The respiratory infection assessment should have been performed within 3 days of symptom onset or worsening. If this was not possible or the visit for the assessment was missed, it could have been performed within 12 days of symptom onset or worsening.

If any signs or symptoms of respiratory infection were present, then an NP sample was to be collected from the participant for RT-PCR testing.

Study Participants

Healthy male and female infants who had a chronological age from birth up to 1 year and were entering their first RSV season at the time of consent were enrolled in this study.

Treatments

Table 7. Study interventions

Arm Name	Arm Type	Inter-vention Name	Type	Dose Formu-lation	Unit Dose Strength	Dosage Level	Route of Admini-stration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
MK-1654	Experimental	MK-1654	Biological/ Vaccine	Vial	150 mg/mL	105 mg	IM	Single administration	Test Product	IMP	Sponsor
Placebo	Placebo Comparator	Placebo	Other	Sterile Solution	0 mg/mL	0 mg	IM	Single administration	Placebo	IMP	Sponsor or local
EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; NIMP/AxMP-noninvestigational/auxiliary medicinal product. Placebo=Sterile saline 0.9% sodium chloride injection. Equivalent volumes of saline will be used to correspond with the respective dose level. The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.											

Participants should have received recommended childhood vaccines in alignment with local/national immunization guidelines.

Objectives

Primary objective

- 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%).

- To evaluate the safety and tolerability of MK-1654 compared to placebo as assessed by the proportion of participants experiencing AEs.

Secondary objectives

- 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%).

- 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.

Tertiary/Exploratory objectives

- To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated severe MALRI (outpatient and inpatient) from Days 1 through 150 postdose.
- To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated hospitalization from Days 1 through 180 postdose.
- To estimate the incidence of MALRI (outpatient and inpatient) due to any cause from Days 1 through 150 postdose for the MK-1654 and placebo groups.
- To describe the incidence of RSV associated MALRI (outpatient and inpatient) from Days 365 through 515 postdose for the MK-1654 and placebo groups.
- To describe the incidence of RSV associated hospitalization from Days 365 through 515 postdose for the MK-1654 and placebo groups.
- To describe the serum PK concentration of MK-1654 at Days 7, 150, and 240 postdose.
- To estimate the incidence and magnitude of ADA to MK-1654 on Day 1 (predose) and Days 150, 240, 365, and 515 postdose.
- To estimate the level of SNA to RSV A on Day 1 (predose) and Days 7, 150, 240, 365, and 515 postdose.
- To determine RSV F gene sequence in NP samples from infants infected with RSV who received MK-1654 or placebo.

Outcomes/endpoints

Primary endpoints

Efficacy: Number of participants with RSV-MALRI in the MK- 1654 and placebo groups from Days 1 through 150 postdose.

RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting:

Table 8. Respiratory syncytial virus (RSV)-associated medically attended lower respiratory infection (MALRI) diagnostic criteria

Signs/Symptoms	Indicators of LRI/Severity	RSV
Endpoint definition requires at least 1 from each column seen in an outpatient or inpatient clinical setting (outpatient clinic, clinical study visit, Emergency Department, urgent care center, or hospital) and confirmed or observed by the investigator.		
• Cough • Difficulty breathing	• Wheezing • Chest wall in-drawing/Retractions • Rales/Crackles • Hypoxemia (SpO_2 <95% on room air at sea level, <92% on room air at altitude ≥1800 m)[a] • Tachypnea (RR ≥60 breaths per minute for <2 months of age; ≥50 breaths per minute for 2 to 12 months of age; or ≥40 breaths per minute for >12 to 24 months of age) • Dehydration due to respiratory symptoms	• RSV-positive RT-PCR NP sample (collected within 12 days of symptom onset or worsening)

LRI=lower respiratory infection; MALRI=medically attended lower respiratory infection; NP=nasopharyngeal; RR=respiratory rate; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase-polymerase chain reaction; SpO_2=oxygen saturation as measured by pulse oximetry.

[a] For severe MALRI: Severe hypoxemia (SpO_2 <90% on room air at sea level; <87% on room air at altitude ≥1800 m) or the need for high flow nasal cannula, oxygen mask, or mechanical ventilatory support.

Safety: Number of participants experiencing solicited injection-site AEs from Days 1 through 5 postdose, solicited daily body temperature to identify fever 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, and SAEs through the duration of study participation.

Secondary efficacy endpoints

- Number of participants with RSV hospitalization in the MK-1654 and placebo groups from Days 1 through 150 postdose.

  RSV-associated hospitalization, defined as the following:

  - Hospital admission for respiratory illness;

  AND

  - RSV-positive RT-PCR NP sample

- Number of participants with RSV-MALRI in the MK-1654 and placebo groups from Days 1 through 180 postdose.

  - RSV-associated MALRI (outpatient and inpatient), defined as above (see *Primary endpoint*)

Pharmacokinetics Endpoints

The tertiary PK endpoints are the serum PK concentration of MK-1654 at Days 7, 150, and 240 postdose.

Pharmacodynamics Endpoints

The tertiary pharmacodynamics endpoints are SNA titers against RSV A at Day 1 (predose) and Days 7, 150, 240, 365, and 515 postdose.

Immunogenicity Endpoints

The tertiary immunogenicity endpoints are ADA to MK-1654 at Day 1 (predose) and Days 150, 240, 365, and 515 postdose.

Sample size

The sample size of approximately 3300 was chosen to ensure collection of adequate safety information. Under the assumptions of 10% per season incidence of RSV-associated MALRI in the placebo group, 70% efficacy and an attrition rate of 5% the power to demonstrate that the efficacy of MK-1654 is larger than 25% compared to placebo as calculated to be >95%. Power calculations were done via a simulation study for the modified Poisson regression.

With the assumption of 2% incidence of RSV-associated hospitalisation in the placebo group and 70% efficacy against RSV-associated hospitalisation compared to placebo the power to demonstrate efficacy >0% in this secondary endpoint was calculated as larger than 93.6% using the same methodology.

Randomisation and blinding (masking)

Randomization

Intervention randomization occurred centrally using an IRT system. There were 2 study intervention arms. Participants were assigned randomly in a 2:1 ratio to MK-1654 or placebo.

Stratification

Intervention randomization was stratified by region (northern hemisphere, southern hemisphere), gestational age (early and moderate preterm infants ≥29 to <35 weeks gestational age, late preterm and full-term infants ≥35 weeks gestational age), chronological age at the time of consent (<6 months of age, ≥6 months of age)

Blinding

A double-blinding technique was used. MK-1654 and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel otherwise not involved in the conduct of the study. Unblinded study personnel should not have had contact with participants for any study-related procedures/assessments post-dose, including all safety follow-up procedures. The participant, the investigator, and Sponsor personnel or delegate(s) who were involved in the study intervention administration or clinical evaluation of the participants were unaware of the intervention assignments.

Statistical methods

Analysis Sets

The primary efficacy analysis was conducted in the full analysis set (FAS) population which included all study participants who received a dose of study intervention.

Supportive analyses were conducted in the per protocol (PP) efficacy population. The PP efficacy population consisted of subjects who received one dose of study medication according to

randomisation and had at least one follow-up visit or phone call for assessment of RSV disease and did not have protocol deviations that might interfere with efficacy assessment.

Estimation

Modified Poisson regression to estimate the risk ratio (RR) and confidence intervals. Efficacy and CI was then calculated as 100 * (1-RR) from this estimates. The model included treatment group and stratification factors as covariates. If the estimator did not converge covariates were stepwise omitted.

Missing Data

Missing data was not imputed in either study.

Multiplicity

The primary and secondary efficacy endpoints were tested in a hierarchical manner. An interim analysis with the possibility of stopping early for efficacy was not planned.

Results

Participant flow

A total of 3632 participants were randomized across 192 study sites in 22 countries.

Table 9. Disposition of participants (all randomized participants)

	MK-1654 105 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	2,421		1,211		3,632	
Dosed at Day 1						
MK-1654 105 mg	2,411	(99.6)	1	(0.1)	2,412	(66.4)
Placebo	0	(0.0)	1,202	(99.3)	1,202	(33.1)
Trial Disposition						
Completed	2,104	(86.9)	1,049	(86.6)	3,153	(86.8)
Discontinued	159	(6.6)	83	(6.9)	242	(6.7)
Death	6	(0.2)	3	(0.2)	9	(0.2)
Lost To Follow-Up	65	(2.7)	33	(2.7)	98	(2.7)
Physician Decision[a]	12	(0.5)	4	(0.3)	16	(0.4)
Randomized By Mistake Without Study Treatment	0	(0.0)	1	(0.1)	1	(0.0)
Withdrawal By Parent/Guardian	75	(3.1)	40	(3.3)	115	(3.2)
Other	1	(0.0)	2	(0.2)	3	(0.1)
Status Not Recorded	158	(6.5)	79	(6.5)	237	(6.5)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.

[a] One participant discontinued due to Physician Decision and died 402 days after study discontinuation. The death was recorded in the safety database and is included in the relevant safety tables.

Source: [P004V01MK1654: adam-adsl; adex]

Table 10. Summary of follow-up visits (all dosed participants)

	MK-1654 105 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in RSV season 1 population	**2,411**		**1,203**		**3,614**	
Day 1 Predose	2,411	(100.0)	1,203	(100.0)	3,614	(100.0)
Day 7	2,400	(99.5)	1,196	(99.4)	3,596	(99.5)
Day 42	2,384	(98.9)	1,187	(98.7)	3,571	(98.8)
Day 90	2,365	(98.1)	1,186	(98.6)	3,551	(98.3)
Day 150	2,339	(97.0)	1,167	(97.0)	3,506	(97.0)
Day 240	2,311	(95.9)	1,159	(96.3)	3,470	(96.0)
Day 365	2,127	(88.2)	1,064	(88.4)	3,191	(88.3)
Participants in RSV season 2 population	**1,016**		**502**		**1,518**	
Day 515	994	(97.8)	492	(98.0)	1,486	(97.9)

RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl] [P004V01MK1654: sdtm-sv; suppsv]

The majority (48 of 57) of nonrandomized participants were screen failures who did not satisfy the inclusion criteria or did meet the exclusion criteria.

Recruitment

This study is ongoing; the CSR includes complete efficacy data and safety follow-up through at least 240 days postdose for all participants up to the data cutoff date (04-MAR-2024):

First Participant First Visit	07-APR-2021
Data Cutoff (last participant last visit for this interim CSR)	04-MAR-2024
Last Data Available	01-MAY-2024
Database Lock Date	08-MAY-2024

Clinical investigator study sites were 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, UK, and US. Sites in Israel and Romania did not screen participants.

Conduct of the study

Table 11. Protocol amendments for MK-1654-004

Document	Date of Issue	Overall Rationale
Amendment 5	02-DEC-2022	The key reasons for this amendment were to: 1) allow for over enrollment of participants in the study and 2) allow for local sourcing of placebo.
Amendment 4	01-APR-2022	The primary purpose of this amendment was to: 1) Clarify that blood collection for participants with an anaphylaxis or hypersensitivity AESI of Grade 3 or 4 is to assay for potential ADA to MK-1654, and additional ADA characterization, if indicated; 2) Add China-specific protocol requirements for a separate, additional swab collection for COVID-19 testing.
Amendment 3	29-SEP-2021	The primary purpose of this amendment was to: 1) Provide additional guidance on respiratory infection assessment and nasopharyngeal (NP) sample collection; and 2) Add China-specific protocol requirements.
Amendment 2	23-APR-2021	The purpose of this amendment was to address regional Health Authority feedback.
Amendment 1	08-FEB-2021	The primary purpose of this amendment was to add changes that align with the approved pediatric development plan and changes in severity grading of adverse events, which had been adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
Original Protocol	28-JUL-2020	Not applicable.

Protocol deviations

Table 12. Summary of important protocol deviations (all randomized participants)

	MK-1654 105 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	2,421		1,211		3,632	
with one or more important protocol deviations	319	(13.2)	191	(15.8)	510	(14.0)
with no important protocol deviations	2,102	(86.8)	1,020	(84.2)	3,122	(86.0)
Inclusion/ Exclusion Criteria	**5**	**(0.2)**	**1**	**(0.1)**	**6**	**(0.2)**
Participant enrolled in the trial more than once.	3	(0.1)	0	(0.0)	3	(0.1)
Participant is recommended or eligible to receive palivizumab per local guidelines or professional society recommendations	2	(0.1)	1	(0.1)	3	(0.1)
Informed Consent	**4**	**(0.2)**	**1**	**(0.1)**	**5**	**(0.1)**
Participant had no documented updated consent following a significant change to the consent and/or risk language	4	(0.2)	1	(0.1)	5	(0.1)
Safety Reporting	**30**	**(1.2)**	**18**	**(1.5)**	**48**	**(1.3)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	30	(1.2)	18	(1.5)	48	(1.3)
Study Intervention	**13**	**(0.5)**	**3**	**(0.2)**	**16**	**(0.4)**
Participant received more than or less than the protocol defined dose of 0.7mL of study intervention	8	(0.3)	0	(0.0)	8	(0.2)
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	5	(0.2)	2	(0.2)	7	(0.2)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	1	(0.0)	1	(0.1)	2	(0.1)
Trial Procedures	**279**	**(11.5)**	**178**	**(14.7)**	**457**	**(12.6)**
NP swab was required and collected per protocol but an issue impacting the sample caused it to become non-viable with no results reported.	23	(1.0)	14	(1.2)	37	(1.0)
Participant had a Grade 3 or 4 rash AESI but a dermatology consultation was not completed	1	(0.0)	0	(0.0)	1	(0.0)
Participant had a rash AESI but photographs were not taken during assessment	2	(0.1)	1	(0.1)	3	(0.1)
Participant had respiratory infection symptoms and an appropriate study NP swab was required but not obtained per protocol.	255	(10.5)	166	(13.7)	421	(11.6)
Participant was not observed post dose as required per protocol (0 minutes)	1	(0.0)	0	(0.0)	1	(0.0)
Participants legally acceptable representative failed to enter any data as required per protocol into the ediary from Days 1-42 postdose (0% compliance)	1	(0.0)	0	(0.0)	1	(0.0)
Participants legally acceptable representative reported an AESI but a site assessment was not performed according to the protocol	1	(0.0)	0	(0.0)	1	(0.0)

Every participant is counted a single time for each applicable row and column.

Source: [P004V01MK1654: adam-adsl] [P004V01MK1654: sdtm-dv; suppdv]

Site-specific GCP non-compliance

- Three participants from 2 families were enrolled by their parents/ legally authorized representative(s) (LAR[s]) into the same study, MK 1654-004, at 2 different sites and were dosed twice with study intervention (clesrovimab or placebo). The parents/LAR(s) did not inform the respective study staff/investigators at this site that their infants were already participating in the same study at another site.
- Study staff failed to follow the protocol-required blinding plan for all 5 participants. Blinded study staff completed protocol-specific forms intended to be completed only by the unblinded Study Coordinator (SC). The information was given from unblinded SC to the blinded SC 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. This misconduct was discovered during routine monitoring activities.

Baseline data

Table 13. Participant characteristics (all dosed participants)

	MK-1654 105 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	2,411		1,203		3,614	
Sex						
Male	1,228	(50.9)	617	(51.3)	1,845	(51.1)
Female	1,183	(49.1)	586	(48.7)	1,769	(48.9)
Age at Randomization (Months)						
<6	1,923	(79.8)	964	(80.1)	2,887	(79.9)
≥6 to <9	383	(15.9)	192	(16.0)	575	(15.9)
≥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 to 12		0 to 12		0 to 12	
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	(0.0)	1	(0.1)	2	(0.1)
White	1,082	(44.9)	550	(45.7)	1,632	(45.2)
Missing[a]	9	(0.4)	5	(0.4)	14	(0.4)
Ethnicity						
Hispanic Or Latino	682	(28.3)	335	(27.8)	1,017	(28.1)
Not Hispanic Or Latino	1,660	(68.9)	834	(69.3)	2,494	(69.0)
Not Reported	17	(0.7)	10	(0.8)	27	(0.7)
Unknown	49	(2.0)	23	(1.9)	72	(2.0)
Missing	3	(0.1)	1	(0.1)	4	(0.1)
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)	1,989	(82.5)	994	(82.6)	2,983	(82.5)

Region at Randomization						
Northern Hemisphere	1,650	(68.4)	814	(67.7)	2,464	(68.2)
Southern Hemisphere	761	(31.6)	389	(32.3)	1,150	(31.8)
Climate at Randomization						
Tropical/Sub-tropical	459	(19.0)	233	(19.4)	692	(19.1)
Temperate	1,952	(81.0)	970	(80.6)	2,922	(80.9)
Body Weight at Randomization (kg)						
Participants with data	2,411		1,203		3,614	
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)						
Participants with data	2,411		1,203		3,614	
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	

[a] Includes 8 participants from South Africa who have race reported as "Colored" which is not a standard category on the form.
SD=Standard deviation.

Source: [P004V01MK1654: adam-adsl]

Medical history

The 4 most frequently reported medical history conditions overall (by preferred term) were jaundice neonatal (10.7%), premature baby (8.1%), low birth weight baby (6.4%), respiratory distress (4.0%).

Numbers analysed

Table 14. Participant accounting for efficacy analyses in the full analysis set population (all randomized participants)

	MK-1654 105 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	2,421		1,211		3,632	
Participants included in analyses	2,398	(99.0)	1,201	(99.2)	3,599	(99.1)
Reasons for exclusions from analyses[a]						
Participant-level exclusions	23	(1.0)	10	(0.8)	33	(0.9)
Enrolled in the trial more than once	3	(0.1)	0	(0.0)	3	(0.1)
Improper storage of study treatment	5	(0.2)	2	(0.2)	7	(0.2)
Randomized but not treated	10	(0.4)	8	(0.7)	18	(0.5)
Suspected misconduct	5	(0.2)	0	(0.0)	5	(0.1)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion.

Source: [P004V01MK1654: adam-adsl; adpdev1; adeff]

Table 15. Participant accounting for efficacy analyses in the per-protocol population (all randomized participants)

	MK-1654 105 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	2,421		1,211		3,632	
Participants included in analyses	2,392	(98.8)	1,199	(99.0)	3,591	(98.9)
Reasons for exclusions from analyses[a]						
Participant-level exclusions	29	(1.2)	12	(1.0)	41	(1.1)
Eligible to receive palivizumab	2	(0.1)	1	(0.1)	3	(0.1)
Enrolled in the trial more than once	3	(0.1)	0	(0.0)	3	(0.1)
Improper storage of study treatment	5	(0.2)	2	(0.2)	7	(0.2)
Incorrect treatment	0	(0.0)	1	(0.1)	1	(0.0)
Randomized but not treated	10	(0.4)	8	(0.7)	18	(0.5)
Received more than or less than the protocol defined dose	8	(0.3)	0	(0.0)	8	(0.2)
Suspected misconduct	5	(0.2)	0	(0.0)	5	(0.1)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion.

Source: [P004V01MK1654: adam-adsl; adpdev1; adeff]

Outcomes and estimation

Primary Efficacy Endpoint

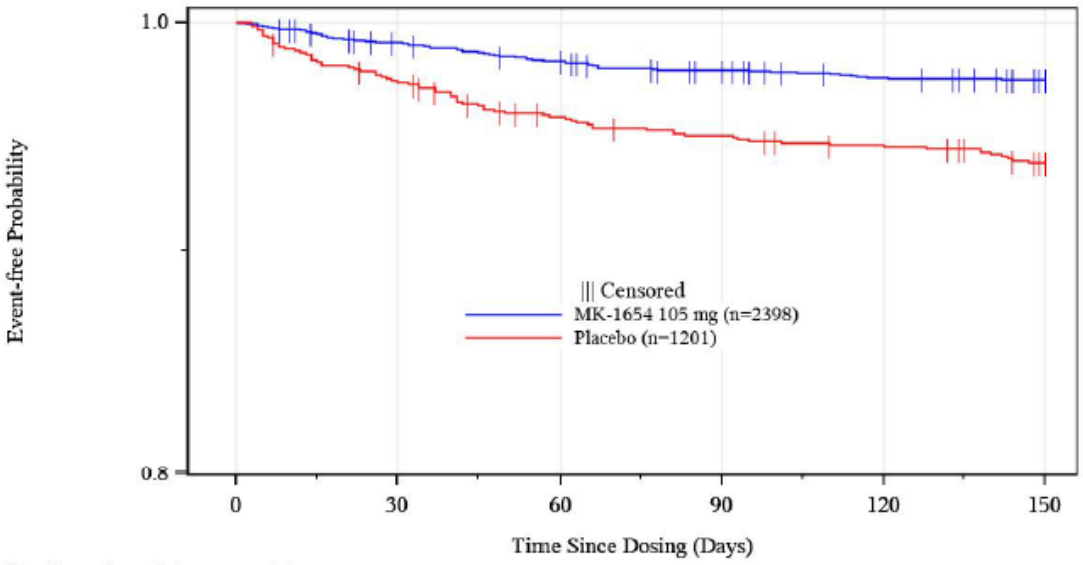
Table 16. Analysis of RSV-associated outpatient and inpatient MALRI Days 1 to 150 Postdose (Full Analysis Set Population)

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%)	
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	Estimate (95% CI)[c]	p-Value[c] (1-sided)
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 Type										
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)	

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression 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. For the analyses by RSV type, the model included only the term of treatment group assignment. One-sided p-value was estimated by an exact method. The statistical criterion for success requires the lower bound of the 95% CI of efficacy to be greater than 25%.
N=Number of participants randomized and dosed with MK-1654 105 mg or placebo.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

Figure 24. Kaplan-Meier Plot of Time from dosing to first RSV-associated Outpatient or Inpatient MALRI Days 1 to 150 Postdose (Full Analysis Set)



Number of participants at risk

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

Number of events inside period

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

Source: [P004V01MK1654: adam-adsl; adeff]

Consistent with the results in the FAS population, administration of clesrovimab reduced the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose compared with placebo in the PP efficacy population.

Secondary Efficacy Endpoints

RSV-associated Hospitalization From Days 1 Through 150 Postdose

Table 17. Analysis of RSV-associated hospitalization Days 1 to 150 Postdose (Full Analysis Set)

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%)	
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	Estimate (95% CI)[c]	p-Value[c] (1-sided)
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 Type										
RSV A	2398	4	11879.9	0.002	1201	12	5916.0	0.010	83.4 (48.5, 94.6)	
RSV B	2398	5	11874.2	0.002	1201	16	5898.7	0.014	84.5 (57.6, 94.3)	

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days.

[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression 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 analyses by RSV type, the model included only the term of treatment group assignment. One-sided p-value was estimated by an exact method. The statistical criterion for success requires the lower bound of the 95% CI of efficacy to be greater than 0%.

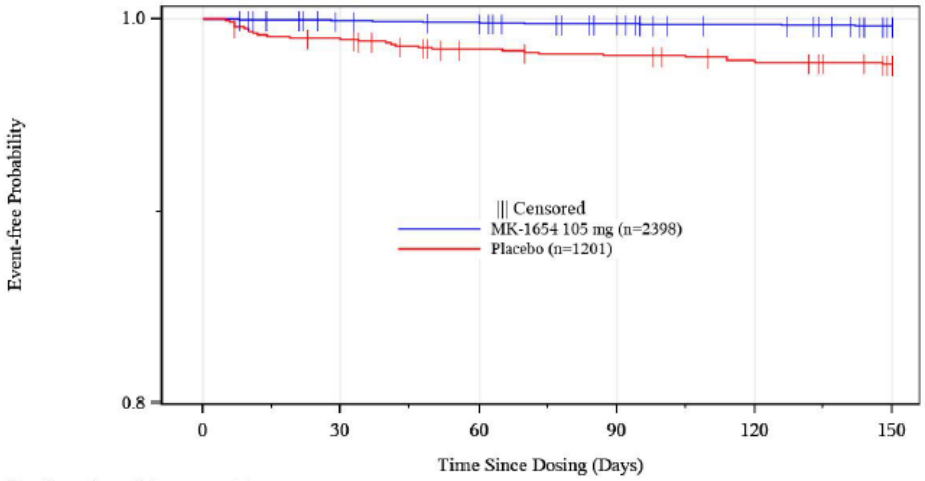
N=Number of participants randomized and dosed with MK-1654 105 mg or placebo.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

Figure 25. Kaplan-Meier Plot of Time from dosing to first RSV-associated hospitalization Days 1 to 150 Postdose (Full Analysis Set)



Number of participants at risk

MK-1654 105 mg (n=2398)	2398	2385	2381	2368	2360	2345
Placebo (n=1201)	1201	1187	1172	1166	1160	1152

Number of events inside period

MK-1654 105 mg (n=2398)	2	2	2	1	2	0
Placebo (n=1201)	12	7	4	3	2	0

Source: [P004V01MK1654: adam-adsl; adeff]

RSV-associated MALRI From Days 1 Through 180 Postdose

Table 18. Analysis of RSV-associated outpatient and inpatient MALRI Days 1 to 180 Postdose (Full Analysis Set Population)

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 6 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 6 Months[b]	
RSV-associated Outpatient and Inpatient MALRI	2398	64	13970.8	0.027	1201	77	6813.6	0.068	59.5 (43.3, 71.1)
By RSV Type									
RSV A	2398	32	14096.6	0.014	1201	29	7019.0	0.025	45.1 (9.0, 66.8)
RSV B	2398	34	14098.9	0.014	1201	48	6928.1	0.042	65.2 (45.9, 77.6)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Six months is defined as 180 days.

[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression 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. For the analyses by RSV type, the model included only the term of treatment group assignment.

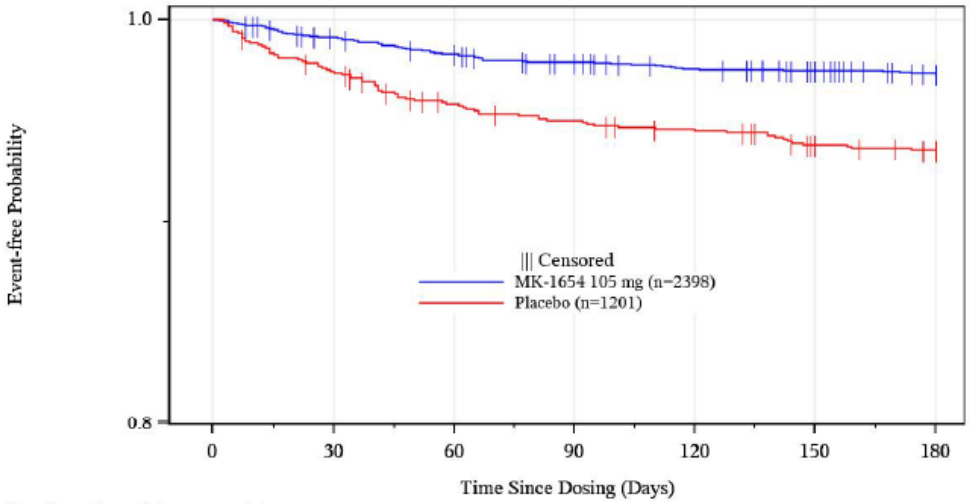
N=Number of participants randomized and dosed with MK-1654 105 mg or placebo.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

Figure 26. Kaplan-Meier Plot of Time from dosing to first RSV-associated Outpatient or Inpatient MALRI Days 1 to 180 Postdose (Full Analysis Set)



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

Exploratory Efficacy Endpoints in RSV Season 1

RSV-associated Severe MALRI

Table 19. Analysis of RSV-associated outpatient and inpatient severe MALRI Days 1 to 150 Postdose (Full Analysis Set Population)

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
RSV-associated Outpatient and Inpatient Severe MALRI	2398	2	11882.0	0.001	1201	12	5906.4	0.010	91.7 (62.9, 98.1)
By RSV Type									
RSV A	2398	1	11885.5	0.000	1201	4	5937.7	0.003	87.5 (-11.8, 98.6)
RSV B	2398	1	11885.9	0.000	1201	8	5924.5	0.007	93.8 (50.2, 99.2)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or placebo.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

The efficacy relative to placebo was 91.7% (95% CI: 62.9%, 98.1%) for both timeframes (from Days 1 through 150 postdose and from Days 1 through 180 postdose).

RSV-associated LRI Hospitalization

Table 20. Analysis of RSV-associated LRI hospitalization Days 1 to 150 postdose (Full Analysis Set Population)

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
RSV-associated LRI Hospitalization	2398	5	11874.1	0.002	1201	27	5862.8	0.023	90.9 (76.2, 96.5)
By RSV Type									
RSV A	2398	2	11882.5	0.001	1201	12	5916.0	0.010	91.7 (62.9, 98.1)
RSV B	2398	3	11880.9	0.001	1201	15	5902.5	0.013	90.1 (65.7, 97.1)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or placebo.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; LRI=Lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

The efficacy relative to placebo was 91.2% (95% CI: 77.2%, 96.6%) from Days 1 through 180 postdose.

Exploratory Efficacy Endpoint in RSV Season 2

Table 21. Summary of RSV-associated outpatient and inpatient MALRI Days 365 to 515 Postdose (Full Analysis Set Population)

Endpoint	MK-1654 105 mg (N=1016)				Placebo (N=502)			
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]
RSV-associated Outpatient and Inpatient MALRI	1008	53	4851.9	0.055 (0.041, 0.071)	501	26	2423.4	0.054 (0.035, 0.079)
By RSV Type								
RSV A	1008	25	4951.4	0.025 (0.016, 0.037)	501	14	2463.6	0.028 (0.016, 0.048)
RSV B	1008	29	4936.5	0.029 (0.020, 0.042)	501	13	2463.0	0.026 (0.014, 0.045)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days. 95% CI of incidence rate was estimated by exact Poisson confidence limits.
N=Number of participants who entered RSV season 2 follow-up.
n=Number of participants who entered RSV season 2 and are eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

The incidence rate of RSV-associated hospitalization was generally comparable between the MK-1654 and placebo groups from Days 365 through 515 postdose.

The incidence rates of RSV-associated severe MALRI (outpatient and inpatient) were low (≤0.002) in either intervention group from Days 365 through 515 postdose.

Ancillary analyses

Pre-defined subgroup analyses

*Table 22. Analysis of RSV-associated Outpatient and Inpatient MALRI **by gestational age** group Day 1 to 150 postdose (full analysis set)*

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
Early and Moderate preterm Infants									
RSV-associated Outpatient and Inpatient MALRI	417	9	2027.3	0.022	208	21	957.6	0.110	79.8 (55.5, 90.8)
By RSV Type									
RSV A	417	5	2039.5	0.012	208	7	1003.9	0.035	64.8 (-11.5, 88.9)
RSV B	417	4	2046.8	0.010	208	14	983.5	0.071	86.3 (58.1, 95.5)
Late preterm and full-term Infants									
RSV-associated Outpatient and Inpatient MALRI	1981	51	9658.3	0.026	993	53	4752.9	0.056	52.6 (30.3, 67.8)
By RSV Type									
RSV A	1981	24	9740.7	0.012	993	19	4865.0	0.020	36.9 (-15.4, 65.5)
RSV B	1981	29	9739.3	0.015	993	34	4813.9	0.035	57.8 (30.7, 74.4)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
Early and Moderate preterm Infants refer to infants born ≥29 to <35 weeks gestational age and Late preterm and full-term Infants refer to infants born ≥35 weeks gestational age.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or Placebo.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

*Table 23. Analysis of RSV-associated Outpatient and Inpatient MALRI **by age group** Day 1 to 150 postdose (full analysis set)*

Endpoint	MK-1654 105 mg (N=2411) n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	Placebo (N=1203) n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	Observed Efficacy (%) Estimate (95% CI)[c]
≤2 Weeks of Age[d]									
RSV-associated Outpatient and Inpatient MALRI	99	1	493.7	0.010	56	6	261.1	0.115	91.2 (34.2, 99.6)
By RSV Type									
RSV A	99	0	495.0	0.000	56	2	276.5	0.036	100.0 (-93.9, 100.0)
RSV B	99	1	493.7	0.010	56	4	264.6	0.076	86.6 (-2.9, 99.4)
<6 Months of Age									
RSV-associated Outpatient and Inpatient MALRI	1915	47	9348.9	0.025	963	66	4553.5	0.072	65.3 (49.5, 76.4)
By RSV Type									
RSV A	1915	22	9422.2	0.012	963	24	4694.4	0.026	54.3 (18.1, 75.0)
RSV B	1915	26	9424.5	0.014	963	42	4631.3	0.045	69.6 (49.4, 81.9)
≥6 Months of Age									
RSV-associated Outpatient and Inpatient MALRI	483	13	2336.7	0.028	238	8	1157.0	0.035	19.5 (-101.3, 66.8)
By RSV Type									
RSV A	483	7	2357.9	0.015	238	2	1174.5	0.009	-74.3 (-1064.4, 60.9)
RSV B	483	7	2361.6	0.015	238	6	1166.1	0.026	42.4 (-79.4, 82.6)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days.

[c] Due to convergence issue and/or non-estimable CI using the modified Poisson method, estimate of efficacy was based on the exact binomial method proposed by Chan and Bohidar, and estimate of 95% CI was based on Blaker's exact CI.

[d] The subgroup "≤2 Weeks of Age" is a subset of the subgroup "<6 Months of Age".

N=Number of participants randomized and dosed with MK-1654 105 mg or Placebo.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

*Table 24. Analysis of RSV-associated Outpatient and Inpatient MALRI **by body weight** at randomisation Day 1 to 150 postdose (full analysis set)*

Endpoint	MK-1654 105 mg (N=2411) n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	Placebo (N=1203) n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	Observed Efficacy (%) Estimate (95% CI)[c]
<5 kg Body Weight									
RSV-associated Outpatient and Inpatient MALRI	860	23	4181.4	0.028	428	36	2012.1	0.089	69.3 (47.9, 81.8)
By RSV Type									
RSV A	860	8	4231.9	0.009	428	12	2086.4	0.029	67.1 (19.4, 86.6)
RSV B	860	15	4208.5	0.018	428	24	2048.6	0.059	69.6 (41.8, 84.1)
≥5 kg Body Weight									
RSV-associated Outpatient and Inpatient MALRI	1538	37	7504.2	0.025	773	38	3698.4	0.051	52.0 (24.3, 69.6)
By RSV Type									
RSV A	1538	21	7548.3	0.014	773	14	3782.5	0.019	24.8 (-48.2, 61.9)
RSV B	1538	18	7577.6	0.012	773	24	3748.8	0.032	62.9 (31.5, 79.9)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days.

[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.

N=Number of participants randomized and dosed with MK-1654 105 mg or Placebo.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

*Table 25. Analysis of RSV-associated Outpatient and Inpatient MALRI **by sex** Day 1 to 150 postdose (full analysis set)*

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
Female									
RSV-associated Outpatient and Inpatient MALRI	1176	18	5766.0	0.016	586	32	2803.4	0.057	72.7 (51.2, 84.7)
By RSV Type									
RSV A	1176	6	5804.8	0.005	586	8	2878.4	0.014	62.8 (-7.4, 87.1)
RSV B	1176	13	5782.4	0.011	586	24	2831.5	0.042	73.5 (47.8, 86.5)
Male									
RSV-associated Outpatient and Inpatient MALRI	1222	42	5919.6	0.035	615	42	2907.1	0.072	50.9 (24.4, 68.1)
By RSV Type									
RSV A	1222	23	5975.4	0.019	615	18	2990.4	0.030	36.1 (-18.8, 65.6)
RSV B	1222	20	6003.7	0.017	615	24	2965.9	0.040	58.8 (25.3, 77.3)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or Placebo.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

*Table 26. Analysis of RSV-associated Outpatient and Inpatient MALRI **by hemisphere** at randomisation Day 1 to 150 postdose (full analysis set)*

Endpoint	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
Northern Hemisphere									
RSV-associated Outpatient and Inpatient MALRI	1637	26	8063.0	0.016	812	35	3926.2	0.045	63.8 (39.8, 78.3)
By RSV Type									
RSV A	1637	15	8096.5	0.009	812	13	3997.8	0.016	43.0 (-19.9, 72.9)
RSV B	1637	11	8117.0	0.007	812	22	3967.0	0.028	75.6 (49.5, 88.2)
Southern Hemisphere									
RSV-associated Outpatient and Inpatient MALRI	761	34	3622.6	0.047	389	39	1784.3	0.109	57.1 (31.6, 73.1)
By RSV Type									
RSV A	761	14	3683.6	0.019	389	13	1871.0	0.035	45.3 (-16.9, 74.4)
RSV B	761	22	3669.1	0.030	389	26	1830.4	0.071	57.8 (25.2, 76.2)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or Placebo.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

<u>Post-hoc analyses</u>

In a post hoc analysis, RSV associated MALRI that requires ≥**2 indicators** of LRI/severity (at least 1 indicator of LRI and at least 1 indicator of severity) was assessed.

The diagnostic criteria of this post hoc efficacy MALRI definition required the presence of the following, seen in a clinical setting:

- One or more of the following: rhonchi, rales/crackles, wheezing; AND

- One or more of the following: chest wall in-drawing/retraction, hypoxemia, tachypnea, dehydration due to respiratory symptoms; AND
- RSV-positive RT-PCR NP sample

Analysis of RSV-associated MALRI requiring ≥2 indicators of LRI/severity was performed from Days 1 through 150 and Days 1 through 180 postdose in the FAS population.

Table 27. Post-hoc analysis of RSV-associated outpatient and inpatient MALRI requiring ≥2 indicators of LRI/severity Days 1 to 150 Postdose (Full analysis set population)

	MK-1654 105 mg (N=2411)				Placebo (N=1203)				Observed Efficacy (%) Estimate (95% CI)[c]
Endpoint	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
RSV-associated Outpatient and Inpatient MALRI Requiring ≥ 2 Indicators of LRI/Severity	2398	10	11855.2	0.004	1201	41	5810.8	0.035	88.0 (76.1, 94.0)
By RSV Type									
RSV A	2398	2	11881.5	0.001	1201	11	5920.7	0.009	90.9 (59.1, 98.0)
RSV B	2398	8	11862.9	0.003	1201	30	5845.8	0.026	86.9 (71.3, 94.0)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days.

[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression 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. For the analyses by RSV type, the model included only the term of treatment group assignment.

N=Number of participants randomized and dosed with MK-1654 105 mg or Placebo.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; LRI=Lower respiratory infection; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

MK-1654-007: 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

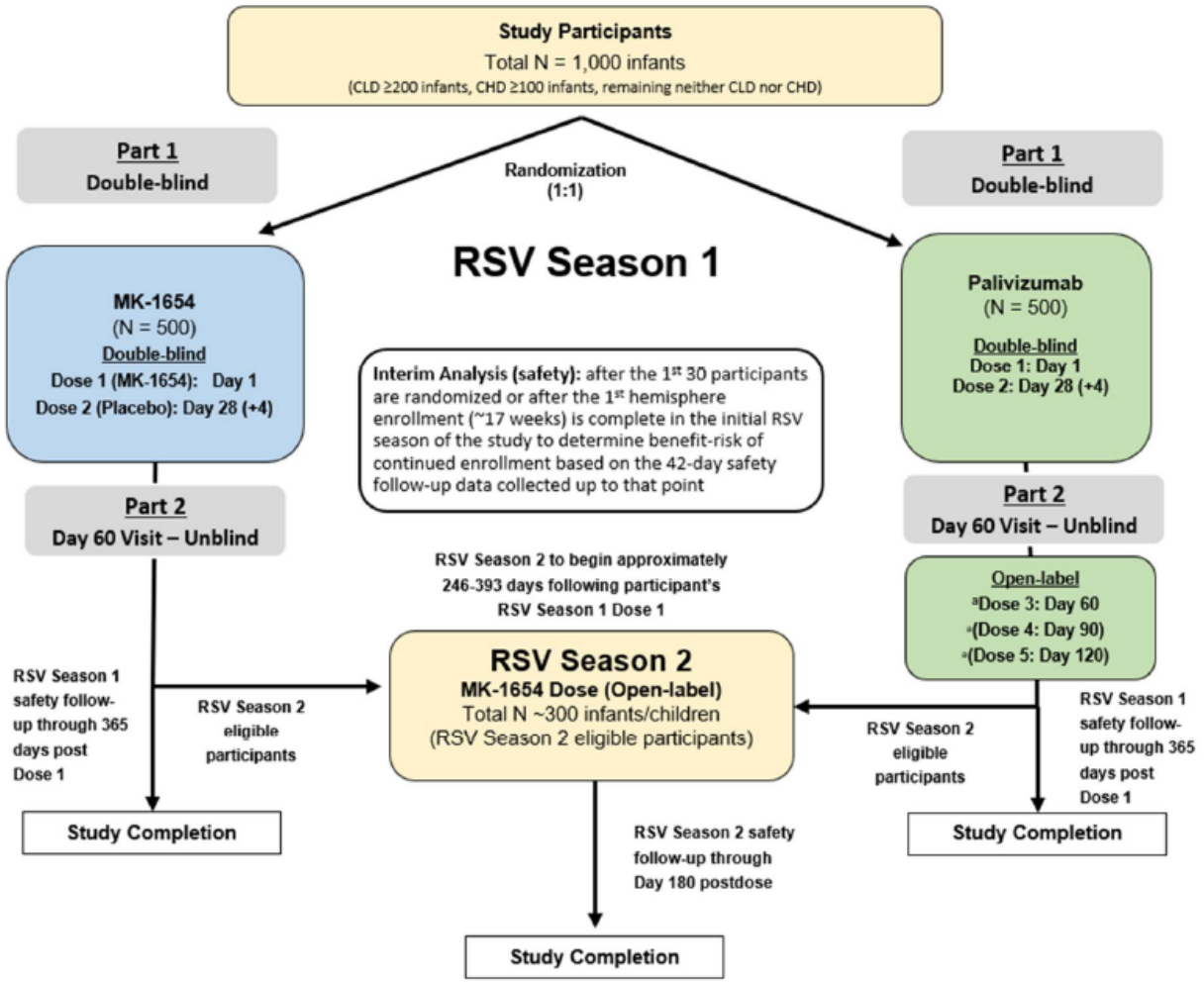
Study code	MK-1654-007
EU CT number	2022-500752-39-00
NCT number	NCT04938830
ISRCT number	
Other identifier(s)	
Location in eCTD	5.3.5.1

Methods

Study MK-1654-007 is a phase 3, partially blinded, randomized, active-controlled, multi-site study to evaluate the safety, tolerability, and efficacy of MK-1654 versus palivizumab and the PK of MK-1654 in infants who are eligible and recommended to receive palivizumab in their first RSV season.

A secondary purpose of the study is to evaluate the safety, efficacy, and PK of a dose of MK-1654 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 RSV who are entering their second RSV season.

Figure 27. Study schema



Abbreviations: CHD=congenital heart disease; CLD=chronic lung disease; N=number of randomized participants; RSV=Respiratory Syncytial Virus

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 post-surgery based on the Sponsor consultation.

Infants 0 through 8 months (ie, up to 8 months and 29 days) of age at the time of consent were to comprise at least 90% of the participants.

All participants, irrespective of treatment group, had safety monitoring (AEs and SAEs), efficacy surveillance to monitor the incidence of RSV-associated MALRI and hospitalization, and blood sample collection.

Study assessments (cf. above section)

At the RSV Season 1 Day 1 visit, potential participants were evaluated to determine whether they meet entry requirements. Potential participants were screened at the study site.

Study Participants

Male/female infants ≤35 weeks gestational age or infants with CLD of prematurity or hemodynamically significant CHD, who had a chronological age from birth up to 1 year and were entering their first RSV season at the time of consent were enrolled in this study.

Early or Moderate Preterm Group (excluding participants with CLD or hemodynamically significant CHD): ≤35 weeks, 0 days gestational age.

CLD/CHD Group: CLD Participants have CLD of prematurity, also known as bronchopulmonary dysplasia, CHD Participants have hemodynamically significant CHD

Treatments

Table 28. Trial intervention

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Administration	Treatment Regimen	Use	IMP/ NIMP	Sourcing
MK-1654	Experimental	MK-1654	Biological/ Vaccine	Vial	150 mg/mL	105 mg	IM	Single dose in RSV Season 1[a] (Day 1 visit)	Experimental	IMP	Sponsor
MK-1654	Experimental	Placebo	Other	Vial	0 mg/mL	0 mg	IM	Single dose in RSV Season 1 (Day 28 visit)	Placebo	IMP	Sponsor or site
MK-1654	Experimental	MK-1654	Biological/ Vaccine	Vial	150 mg/mL	210 mg	IM	Single dose in RSV Season 2[a] (Day 1 visit)	Experimental	IMP	Sponsor
Palivizumab	Active Comparator	Palivizumab	Biological/ Vaccine	Vial	100 mg/mL	15 mg/kg body weight	IM	3 to 5 monthly doses in RSV Season 1[a] (starting at Day 1 visit)	Active comparator	IMP	Sponsor or site
Palivizumab	Active Comparator	MK-1654	Biological/ Vaccine	Vial	150 mg/mL	210 mg	IM	Single dose in RSV Season 2[a] (Day 1 visit)	Experimental	IMP	Sponsor

IM=intramuscular; RSV=respiratory syncytial virus

Placebo=Sterile saline 0.9% sodium chloride injection. Equivalent volumes of saline will be used to correspond with the respective dose level.

Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences in the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

[a] 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 post-surgery based on the Sponsor consultation.

The palivizumab group received subsequent doses of palivizumab every 28 (+4) days through the end of RSV season, for a total of 3 to 5 doses depending on the timing of enrollment relative to the RSV season.

Participants should have received recommended childhood vaccines in alignment with local/national immunization guidelines.

Objectives

Primary objective

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.

This was an estimation study without hypotheses.

Secondary objectives

Secondary Objectives	Secondary Endpoints
- 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 post Dose 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; AND ▪ 1 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
- RSV Season 1: To estimate the incidence of RSV-associated hospitalizations from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.	- RSV-associated hospitalization, defined as the following: ▪ Hospital admission for respiratory illness; AND ▪ 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

Outcomes/endpoints

Primary safety endpoints

• Number of participants with solicited injection-site AEs from Days 1 through 5 after each dose in RSV Season 1.

• Number of participants with fever as measured by solicited daily body temperatures from Days 1 through 5 after each dose in RSV Season 1.

• Number of participants with solicited systemic AEs from Days 1 through 5 after each dose in RSV Season 1.

• Number of participants with anaphylaxis/hypersensitivity AESI from Days 1 through 28 after Dose 1 and Days 1 through 14 after Dose 2 in RSV Season 1.

• Number of participants with rash AESI from Days 1 through 28 after Dose 1 and Days 1 through 14 after Dose 2 in RSV Season 1.

• Number of participants with nonserious AEs from Days 1 through 28 after Dose 1 and 14 days after each subsequent dose in RSV Season 1.

• Number of participants with SAEs through the duration of study participation in RSV Season 1.

Secondary efficacy endpoints

• Number of participants with **RSV-associated MALRI** occurring from Days 1 through 150 post Dose 1 in RSV Season 1.

• Number of participants with **RSV-associated hospitalization** occurring from Days 1 through 150 post Dose 1 in RSV Season 1.

Please see also above.

Sample size

Estimated precision for the efficacy endpoint:

The precision for the estimates of incidences and efficacy were estimated based on a range of assumptions on the observed incidence of RSV-associated MALRI in the MK-1654 and palivizumab groups. The confidence interval was calculated for 1000 simulations of a modified Poisson regression model with the assumption of 10% attrition rate. The 95% confidence intervals for the incidences were calculated based on the exact CI used in the evaluation.

Power for safety endpoints:

Calculations assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 500 participants in the MK-1654 group if the underlying incidence of a SAE is 0.33% (1 of every 303 participants receiving MK-1654). There is a 50% chance of observing at least 1 SAE among 500 participants in the MK-1654 group if the underlying incidence of a SAE is 0.14% (1 of every 714 participants receiving MK-1654). If no SAEs are observed among the 500 participants in the MK-1654 group, this study will provide 97.5% confidence that the underlying percentage of participants with a SAE is <0.74% (1 in every 136 participants in the MK-1654 group).

Randomisation and blinding (masking)

Randomisation

Intervention randomization occurred centrally using an IRT system. There were 2 study intervention arms. Participants were assigned randomly in a 1:1 ratio to MK-1654 or palivizumab.

Intervention randomization was stratified according to the following factors:

1. Region

- Northern Hemisphere

- Southern Hemisphere

2. Participant condition:

- CLD (≥200 infants)
- CHD (≥100 infants)
- Neither CLD nor CHD <29 weeks gestational age
- Neither CLD nor CHD ≥29 weeks gestational age

Blinding

In Part 1 of this study (up to the Day 60 visit), a double-blinding technique will be used. MK-1654, palivizumab, and placebo were prepared and administered in a blinded fashion by an unblinded pharmacist or medically qualified study personnel not otherwise involved in the conduct of the study. Unblinded study personnel should not have had contact with participants for any study-related procedures/assessments post dose (prior to unblinding), including all safety follow-up procedures. The participant's legally acceptable representative, the investigator(s), and Sponsor personnel or delegate(s) were unaware of the study intervention assignments.

Part 2 of this study (time of unblinding through duration of participation in the study) was conducted as open-label. Therefore, the Sponsor, investigator, and participant/participant's legally acceptable representative knew the intervention administered.

Statistical methods

Estimation

Estimations used a modified Poisson regression to estimate the risk ratio (RR) and confidence intervals. Efficacy and CI were then calculated as 100 * (1-RR) from this estimates. The model included the log of the follow-up time as an offset term to account for different follow-up time between participants. The model included treatment group and stratification factors as covariates. If the estimator did not converge covariates were stepwise omitted.

Missing Data

Missing data was not imputed in either study.

Multiplicity

In study 007 the primary objective was to assess safety and tolerability. For the efficacy endpoints no formal hypothesis testing with success criteria were defined and therefore no adjustment for multiplicity was needed.

Results

Participant flow

RSV Season 1

This study is ongoing; the results presented in this interim CSR for regulatory submission are based on data available up to the data cutoff (05-FEB-2024; LPLV for this interim CSR) for participants who were enrolled by 21-DEC-2023 and who had at least 42 days of safety data available in RSV Season 1.

Table 29. Disposition of participants (all randomised participants; RSV Season 1)

	MK-1654 105 mg		Palivizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	450		451		901	
Dosed with						
Dose 1 (Day 1)	446	(99.1)	450	(99.8)	896	(99.4)
Dose 2[a] (Day 28)	432	(96.0)	445	(98.7)	877	(97.3)
Dose 3 (Day 60)	0	(0.0)	429	(95.1)	429	(47.6)
Dose 4 (Day 90)	0	(0.0)	326	(72.3)	326	(36.2)
Dose 5 (Day 120)	0	(0.0)	240	(53.2)	240	(26.6)
Unscheduled[b]	3	(0.7)	2	(0.4)	5	(0.6)
Trial Disposition						
Completed[c]	228	(50.7)	230	(51.0)	458	(50.8)
Discontinued	35	(7.8)	31	(6.9)	66	(7.3)
Death	8	(1.8)	4	(0.9)	12	(1.3)
Lost To Follow-Up	7	(1.6)	6	(1.3)	13	(1.4)
Physician Decision	2	(0.4)	1	(0.2)	3	(0.3)
Randomized By Mistake Without Study Treatment	1	(0.2)	1	(0.2)	2	(0.2)
Withdrawal By Parent/Guardian	17	(3.8)	19	(4.2)	36	(4.0)
Status Not Recorded	187	(41.6)	190	(42.1)	377	(41.8)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.

[a] Participants in the MK-1654 group received placebo at Dose 2.

[b] Participants who receive an additional unscheduled dose of study treatment after undergoing ECMO or cardiopulmonary bypass during the RSV season.

[c] Participants who are continuing in the study in RSV Season 2 are counted under the "Completed" category for RSV Season 1.

ECMO=Extra-corporeal membrane oxygenation; RSV=Respiratory syncytial virus.

Table 30. Summary of follow-up visits (all dosed participants, RSV Season 1)

	MK-1654 105 mg		Palivizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	446		450		896	
Visit						
Day 1 Predose	446	(100.0)	450	(100.0)	896	(100.0)
Day 7	439	(98.4)	446	(99.1)	885	(98.8)
Day 28	434	(97.3)	445	(98.9)	879	(98.1)
Day 60	424	(95.1)	432	(96.0)	856	(95.5)
Day 150	349	(78.3)	358	(79.6)	707	(78.9)
Day 240	310	(69.5)	314	(69.8)	624	(69.6)

RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl] [P007V01MK1654: sdtm-sv; suppsv]

All of the 16 nonrandomized participants were screen failures who did not satisfy the inclusion criteria or did meet the exclusion criteria.

Recruitment

This study is ongoing; the interim CSR is based on data available up to the data cutoff (05-FEB-2024; LPLV for this interim CSR) for participants who were enrolled by 21-DEC-2023 and who had at least 42 days of safety data available in RSV Season 1:

First Participant First Visit	30-NOV-2021
Data Cutoff (last participant last visit for this interim CSR)	05-FEB-2024
Last Data Available	07-MAY-2024
Database Lock Date	08-MAY-2024

Clinical investigator study sites were/are located in 27 countries: Australia, Canada, Chile, Colombia, Czech Republic, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Malaysia, Mexico, New Zealand, Norway, Peru, Puerto Rico, Singapore, South Africa, Spain, Taiwan, Thailand, Türkiye, United Kingdom, and United States.

Conduct of the study

Changes in the conduct of the study implemented by protocol amendments are summarized in the table below:

Table 31. Protocol amendments for MK-1654-007

Document	Date of Issue	Overall Rationale
Amendment 2	18-MAY-2022	The primary purpose of this amendment was to add requirements specific to the Czech Republic.
Amendment 1	23-FEB-2022	The primary purpose of this amendment was to: 1) Specify enrollment targets for different age groups and 2) provide clarification on respiratory infection assessment and nasopharyngeal (NP) sample collection.
Original Protocol	17-MAY-2021	Not applicable

Protocol deviations

Table 32. Summary of important protocol deviations (all randomized participants, RSV Season 1)

	MK-1654 105 mg		Palivizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	450		451		901	
with one or more important protocol deviations	105	(23.3)	212	(47.0)	317	(35.2)
with no important protocol deviations	345	(76.7)	239	(53.0)	584	(64.8)
Informed Consent	**3**	**(0.7)**	**2**	**(0.4)**	**5**	**(0.6)**
Participant had no documented FBR consent but buccal swab was collected.	3	(0.7)	1	(0.2)	4	(0.4)
Participant had no documented initial consent to enter the trial.	0	(0.0)	1	(0.2)	1	(0.1)
Prohibited Medications	**2**	**(0.4)**	**4**	**(0.9)**	**6**	**(0.7)**
Participant has received any marketed vaccine or mAb for the prevention of RSV after randomization	2	(0.4)	4	(0.9)	6	(0.7)
Safety Reporting	**7**	**(1.6)**	**6**	**(1.3)**	**13**	**(1.4)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	7	(1.6)	6	(1.3)	13	(1.4)
Study Intervention	**9**	**(2.0)**	**140**	**(31.0)**	**149**	**(16.5)**
Administering study medication beyond the allowable window: Palivizumab administered beyond 32 days from previous dose.	0	(0.0)	109	(24.2)	109	(12.1)
Participant received incorrect number of doses or incorrect dose volume of MK-1654 or Palivizumab as defined in the protocol.	0	(0.0)	16	(3.5)	16	(1.8)
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	3	(0.7)	17	(3.8)	20	(2.2)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	3	(0.7)	1	(0.2)	4	(0.4)
Participant's blinded study treatment was unblinded during the blinded portion of the trial.	3	(0.7)	7	(1.6)	10	(1.1)
Trial Procedures	**89**	**(19.8)**	**110**	**(24.4)**	**199**	**(22.1)**
Day 3 safety telephone call was not completed following Dose 1, or any subsequent dose of MK-1654.	8	(1.8)	12	(2.7)	20	(2.2)
Incomplete weekly RSV surveillance during the RSV surveillance period (<80% compliance): Days 14 through Day 180 post dose 1 for RSV Seasons 1 and 2. Defined as < 19 weekly contacts where participant's legally acceptable representative responded to eCOA surveillance questions and/or had weekly contact with the site during the RSV surveillance period.	8	(1.8)	6	(1.3)	14	(1.6)
NP swab was required and collected per protocol but an issue impacting the sample caused it to become non-viable with no results reported.	2	(0.4)	5	(1.1)	7	(0.8)
Participant had a rash AESI but photographs were not taken during assessment.	1	(0.2)	0	(0.0)	1	(0.1)
Participant had respiratory infection symptoms and an appropriate study NP swab was required but not obtained per protocol.	39	(8.7)	53	(11.8)	92	(10.2)
Safety data was not collected using the eDiary (0% compliance with eDiary) as required per protocol during:1) the safety follow-up period (Days 1-5) following any blinded dose or 2) the safety follow-up period (Days 1-5) following any subsequent dose of MK 1654	38	(8.4)	48	(10.6)	86	(9.5)

Every participant is counted a single time for each applicable row and column.
RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl] [P007V01MK1654: sdtm-dv; suppdv]

Baseline data

RSV Season 1

Table 33. Participant characteristics (all dosed participants RSV Season 1)

	MK-1654 105 mg		Palivizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	446		450		896	
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)						
<6	409	(91.7)	390	(86.7)	799	(89.2)
≥6 to <9	33	(7.4)	51	(11.3)	84	(9.4)
≥9	4	(0.9)	9	(2.0)	13	(1.5)
Mean	3.0		3.0		3.0	
SD	1.9		2.3		2.1	
Median	2.7		2.3		2.5	
Range	0 to 11		0 to 12		0 to 12	
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	(0.4)	7	(0.8)
White	231	(51.8)	237	(52.7)	468	(52.2)
Ethnicity						
Hispanic Or Latino	138	(30.9)	146	(32.4)	284	(31.7)
Not Hispanic Or Latino	296	(66.4)	296	(65.8)	592	(66.1)
Not Reported	7	(1.6)	5	(1.1)	12	(1.3)
Unknown	5	(1.1)	3	(0.7)	8	(0.9)
Participants Condition						
CLD	124	(27.8)	126	(28.0)	250	(27.9)
CHD	52	(11.7)	49	(10.9)	101	(11.3)
Neither CLD nor CHD less than 29 weeks gestational age	26	(5.8)	24	(5.3)	50	(5.6)
Neither CLD nor CHD greater than or equal to 29 weeks gestational age	244	(54.7)	251	(55.8)	495	(55.2)

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						
Tropical/Sub-tropical	79	(17.7)	81	(18.0)	160	(17.9)
Temperate	367	(82.3)	369	(82.0)	736	(82.1)
Body Weight at Randomization (kg)						
Participants with data	446		450		896	
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	
Length at Randomization (cm)						
Participants with data	443		450		893	
Mean	51.3		50.9		51.1	
SD	6.4		6.7		6.6	
Median	50.0		49.4		50.0	
Range	35.0 to 71.0		35.0 to 74.5		35.0 to 74.5	

CLD=Chronic lung disease; CHD=Congenital heart disease; RSV=Respiratory syncytial virus; SD=Standard deviation.

Numbers analysed

The FAS population served as the primary population for the estimation of efficacy and for the estimation of incidence of RSV-associated disease. The FAS population consists of all randomized participants who receive at least 1 dose of study treatment.

Supportive efficacy analyses were conducted using the PP efficacy population, which consisted of all randomized participants who:

- Received a complete regimen of the correct study intervention corresponding to the treatment group the participants were randomized into,
- Had at least 1 follow-up visit/contact for assessment of RSV disease,
- Did not undergo ECMO or surgical intervention for CHD requiring cardiopulmonary bypass during the efficacy follow-up period (Day 150 or Day 180 post Dose 1 in RSV Season 1), and
- Did not experience a protocol deviation that might interfere with the assessment of protection against RSV infection conferred by clesrovimab at any time during dosing or efficacy follow-up.

Table 34. Participant accounting for efficacy analyses in the full analysis set population (all randomized participants, RSV Season 1)

	MK-1654 105 mg		Palivizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	450		451		901	
Participants included in analyses	443	(98.4)	437	(96.9)	880	(97.7)
Reasons for exclusions from analyses[a]						
Participant-level exclusions	7	(1.6)	14	(3.1)	21	(2.3)
Improper storage of study treatment	3	(0.7)	12	(2.7)	15	(1.7)
No consent	0	(0.0)	1	(0.2)	1	(0.1)
Randomized but not treated	4	(0.9)	1	(0.2)	5	(0.6)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion.
RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adpdev1; adeff]

Table 35. Participant accounting for efficacy analyses in the per-protocol population (all randomized participants, RSV Season 1)

	MK-1654 105 mg		Palivizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	450		451		901	
Participants included in analyses	440	(97.8)	367	(81.4)	807	(89.6)
Reasons for exclusions from analyses[a]						
Participant-level exclusions	10	(2.2)	84	(18.6)	94	(10.4)
Improper storage of study treatment	3	(0.7)	17	(3.8)	20	(2.2)
Incorrect treatment	1	(0.2)	0	(0.0)	1	(0.1)
No consent	0	(0.0)	1	(0.2)	1	(0.1)
One or more palivizumab doses administered out of window	0	(0.0)	36	(8.0)	36	(4.0)
Randomized but not treated	4	(0.9)	1	(0.2)	5	(0.6)
Received ECMO or cardiopulmonary bypass	3	(0.7)	5	(1.1)	8	(0.9)
Received incorrect number of doses or incorrect volume	0	(0.0)	15	(3.3)	15	(1.7)
Received less than three palivizumab doses	0	(0.0)	21	(4.7)	21	(2.3)
Post-deviation exclusions	0	(0.0)	1	(0.2)	1	(0.1)
Received vaccine or mAb for RSV prevention after randomization	0	(0.0)	1	(0.2)	1	(0.1)

Percentages are calculated based on the number of participants randomized.
[a] Participants may have more than one reason for exclusion.
ECMO=Extra-corporeal membrane oxygenation; RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adpdev1; adeff]

Outcomes and estimation

Secondary Efficacy Endpoints

RSV-associated MALRI from Days 1 through 150 Post Dose 1 in RSV Season 1

FAS Efficacy Population

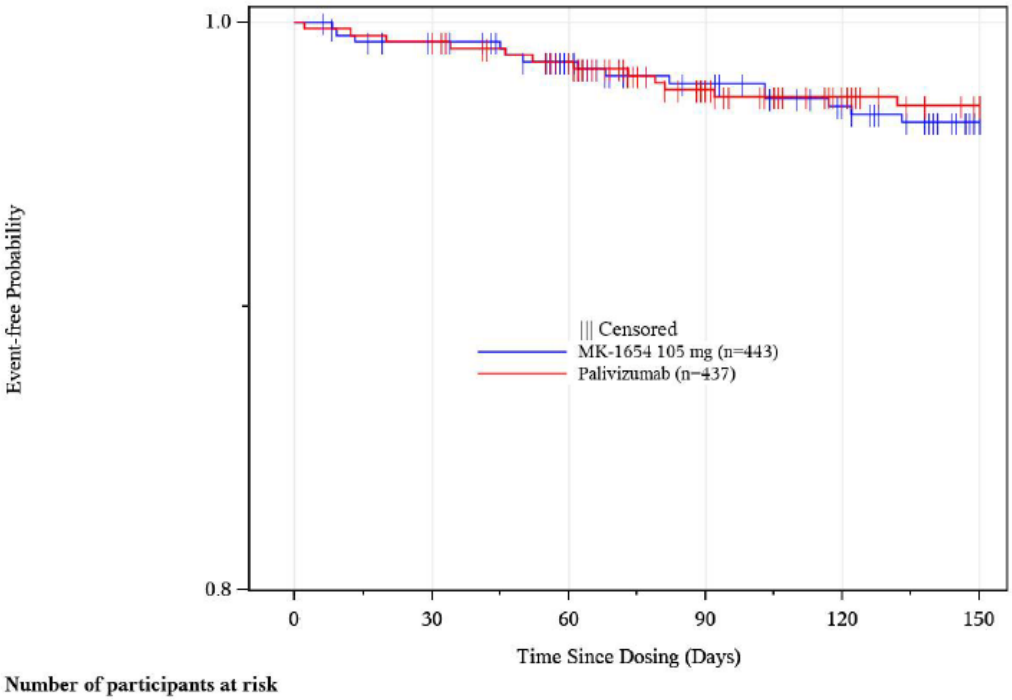
Table 36. Analysis of RSV-associated outpatient and inpatient MALRI post dose 1 days 1 to 150, RSV season 1 (full analysis set population)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
RSV-associated Outpatient and Inpatient MALRI	443	14	1946.9	0.036	437	12	1969.5	0.030	-18.0 (-155.5, 45.5)
By RSV Type									
RSV A	443	6	1968.3	0.015	437	10	1973.1	0.025	39.9 (-65.8, 78.2)
RSV B	443	8	1960.8	0.020	437	2	1998.6	0.005	-307.7 (-1818.1, 13.3)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adeff]

Figure 28. Kaplan-Meier plot of time from first dose to first RSV-associated outpatient and inpatient MALRI post dose 1 days 1 to 150, RSV Season 1 (full analysis set population)



Number of participants at risk

MK-1654 105 mg (n=443)	443	434	395	372	356	332
Palivizumab (n=437)	437	434	419	382	355	342

Number of events inside period

MK-1654 105 mg (n=443)	3	3	3	3	2	0
Palivizumab (n=437)	3	3	4	1	1	0

Sensitivity analysis results, including RSV PCR results tested at both the study central laboratory and local laboratories were consistent with these results (including RSV PCR results from the study central laboratory only).

PP Efficacy Population

Table 37. Analysis of RSV-associated outpatient and inpatient MALRI post dose 1 days 1 to 150, RSV Season 1 (per protocol population)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
RSV-associated Outpatient and Inpatient MALRI	440	14	1931.9	0.036	367	10	1700.1	0.029	-23.2 (-177.9, 45.4)
By RSV Type									
RSV A	440	6	1953.3	0.015	367	9	1700.7	0.026	42.0 (-63.4, 79.4)
RSV B	440	8	1945.8	0.021	367	1	1726.7	0.003	-609.9 (-5564.1, 11.0)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days.

[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.

N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.

n=Number of participants eligible for inclusion in the per protocol efficacy population.

CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Efficacy for RSV-associated MALRI from Days 1 through 150 post Dose 1 or through the end of RSV Season 1, whichever occurred first, was analyzed using the PP efficacy population. These incidence rates were generally comparable between the MK-1654 and palivizumab groups.

RSV-associated Hospitalizations from Days 1 through 150 Post Dose 1 in RSV Season 1

Table 38. Analysis of RSV-associated hospitalization post dose 1 days 1 to 150, RSV season 1 (full analysis set population)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)			
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]
RSV-associated Hospitalization	443	5	1968.9	0.013 (0.004, 0.030)	437	6	1987.3	0.015 (0.006, 0.033)
By RSV Type								
RSV A	443	2	1979.7	0.005 (0.001, 0.018)	437	5	1987.8	0.013 (0.004, 0.029)
RSV B	443	3	1971.4	0.008 (0.002, 0.022)	437	1	2001.7	0.002 (0.000, 0.014)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days. 95% CI of incidence rate was estimated by exact Poisson confidence limits.
N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; RSV=Respiratory syncytial virus.

Sensitivity analysis results, including RSV PCR results tested at both the study central laboratory and local laboratory, were consistent with these results (including RSV PCR results from the study central laboratory only).

PP Efficacy Population

Consistent with the results in the FAS population, the incidence rates of RSV-associated hospitalizations were generally comparable between the MK-1654 group and the palivizumab group from Days 1 through 150 post Dose 1 in RSV Season 1 in the PP efficacy population.

Exploratory Efficacy Endpoints in RSV Season 1

Table 39. Analysis of RSV-associated outpatient and inpatient MALRI post dose 1 days 1 to 180, RSV season 1 (full analysis set population)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 6 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 6 Months[b]	
RSV-associated Outpatient and Inpatient MALRI	443	15	2259.8	0.040	437	12	2291.2	0.031	-26.7 (-171.5, 40.8)
By RSV Type									
RSV A	443	6	2288.7	0.016	437	10	2296.7	0.026	39.8 (-66.1, 78.2)
RSV B	443	9	2278.7	0.024	437	3	2326.2	0.008	-206.2 (-1029.8, 17.0)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Six months is defined as 180 days.
[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.
N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Table 40. Analysis of RSV-associated outpatient and inpatient severe MALRI post dose 1 days 1 to 150, RSV season 1 (full analysis set population)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)			
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]
RSV-associated Outpatient and Inpatient Severe MALRI	443	4	1970.8	0.010 (0.003, 0.026)	437	6	1987.5	0.015 (0.006, 0.033)
By RSV Type								
RSV A	443	1	1981.7	0.003 (0.000, 0.014)	437	5	1988.0	0.013 (0.004, 0.029)
RSV B	443	3	1971.4	0.008 (0.002, 0.022)	437	1	2001.7	0.002 (0.000, 0.014)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days. 95% CI of incidence rate was estimated by exact Poisson confidence limits.
N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Extrapolation

Please refer to the Clinical pharmacology section for the popPK model used to extrapolate efficacy results from Study MK-1654-004 to Study MK-1654-007.

Ancillary analyses

Pre-defined subgroup analysis

Table 41. Summary of RSV-associated outpatient and inpatient MALRI by participant condition post dose 1 Days 1 to 150, RSV Season 1 (full analysis set)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)			
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]
CHD								
RSV-associated Outpatient and Inpatient MALRI	50	4	197.8	0.101 (0.028, 0.259)	48	4	199.5	0.100 (0.027, 0.257)
By RSV Type								
RSV A	50	1	207.5	0.024 (0.001, 0.134)	48	3	200.1	0.075 (0.015, 0.219)
RSV B	50	3	198.4	0.076 (0.016, 0.221)	48	1	210.5	0.024 (0.001, 0.132)
CLD								
RSV-associated Outpatient and Inpatient MALRI	123	4	537.1	0.037 (0.010, 0.095)	123	3	544.4	0.028 (0.006, 0.081)
By RSV Type								
RSV A	123	0	547.9	0.000 (0.000, 0.034)	123	2	547.4	0.018 (0.002, 0.066)
RSV B	123	4	537.1	0.037 (0.010, 0.095)	123	1	550.1	0.009 (0.000, 0.051)
Neither CLD nor CHD <29 Weeks Gestational Age								
RSV-associated Outpatient and Inpatient MALRI	26	0	113.8	0.000 (0.000, 0.162)	24	0	114.1	0.000 (0.000, 0.162)
By RSV Type								
RSV A	26	0	113.8	0.000 (0.000, 0.162)	24	0	114.1	0.000 (0.000, 0.162)
RSV B	26	0	113.8	0.000 (0.000, 0.162)	24	0	114.1	0.000 (0.000, 0.162)
Neither CLD nor CHD ≥29 Weeks Gestational Age								
RSV-associated Outpatient and Inpatient MALRI	244	6	1098.2	0.027 (0.010, 0.059)	242	5	1111.6	0.022 (0.007, 0.052)
By RSV Type								
RSV A	244	5	1099.2	0.023 (0.007, 0.053)	242	5	1111.6	0.022 (0.007, 0.052)
RSV B	244	1	1111.6	0.004 (0.000, 0.025)	242	0	1124.0	0.000 (0.000, 0.016)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days. 95% CI of incidence rate is estimated by exact Poisson confidence limits.
N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Table 42. Summary of RSV-associated outpatient and inpatient MALRI by age group at randomization post dose 1 Days 1 to 150, RSV Season 1 (full analysis set)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)			
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]
<6 Months of Age								
RSV-associated Outpatient and Inpatient MALRI	406	12	1793.3	0.033 (0.017, 0.058)	378	8	1712.5	0.023 (0.010, 0.046)
By RSV Type								
RSV A	406	6	1807.0	0.017 (0.006, 0.036)	378	6	1716.0	0.017 (0.006, 0.038)
RSV B	406	6	1807.2	0.017 (0.006, 0.036)	378	2	1729.2	0.006 (0.001, 0.021)
≥6 Months of Age								
RSV-associated Outpatient and Inpatient MALRI	37	2	153.6	0.065 (0.008, 0.235)	59	4	257.0	0.078 (0.021, 0.199)
By RSV Type								
RSV A	37	0	161.3	0.000 (0.000, 0.114)	59	4	257.0	0.078 (0.021, 0.199)
RSV B	37	2	153.6	0.065 (0.008, 0.235)	59	0	269.4	0.000 (0.000, 0.068)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] One month is defined as 30 days for the total follow-up time calculation.
[b] Five months is defined as 150 days. 95% CI of incidence rate is estimated by exact Poisson confidence limits.
N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.
n=Number of participants eligible for inclusion in the full analysis set population.
CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Table 43. Summary of RSV-associated outpatient and inpatient MALRI by body weight at randomization post dose 1 Days 1 to 150, RSV Season 1 (full analysis set)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)			
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months (95% CI)[b]
<5 kg Body Weight								
RSV-associated Outpatient and Inpatient MALRI	346	10	1531.7	0.033 (0.016, 0.060)	356	9	1602.7	0.028 (0.013, 0.053)
By RSV Type								
RSV A	346	5	1540.8	0.016 (0.005, 0.038)	356	7	1606.3	0.022 (0.009, 0.045)
RSV B	346	5	1542.1	0.016 (0.005, 0.038)	356	2	1624.1	0.006 (0.001, 0.022)
≥5 kg Body Weight								
RSV-associated Outpatient and Inpatient MALRI	97	4	415.2	0.048 (0.013, 0.123)	81	3	366.8	0.041 (0.008, 0.120)
By RSV Type								
RSV A	97	1	427.6	0.012 (0.000, 0.065)	81	3	366.8	0.041 (0.008, 0.120)
RSV B	97	3	418.7	0.036 (0.007, 0.105)	81	0	374.5	0.000 (0.000, 0.049)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days. 95% CI of incidence rate is estimated by exact Poisson confidence limits.

N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Post-hoc Efficacy Analyses

Table 44. RSV-associated MALRI Requiring ⩾2 Indicators of LRI/Severity from Days 1 through 150 postdose1 in RSV Season 1 (full analysis set)

Endpoint	MK-1654 105 mg (N=446)				Palivizumab (N=450)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	n	Number of Cases	Total Follow-up Time in Months[a]	Incidence Rate Over 5 Months[b]	
RSV-associated Outpatient and Inpatient MALRI Requiring ≥ 2 Indicators of LRI/Severity	443	7	1967.1	0.018	437	6	1986.0	0.015	-17.8 (-250.3, 60.4)
By RSV Type									
RSV A	443	3	1977.3	0.008	437	5	1986.6	0.013	39.7 (-152.2, 85.6)
RSV B	443	4	1972.1	0.010	437	1	2001.6	0.002	-306.0 (-3525.6, 54.5)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.

[a] One month is defined as 30 days for the total follow-up time calculation.

[b] Five months is defined as 150 days.

[c] Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method with the use of only the term of treatment group assignment.

N=Number of participants randomized and dosed with MK-1654 105 mg or Palivizumab.

n=Number of participants eligible for inclusion in the full analysis set population.

CI=Confidence interval; LRI=Lower respiratory infection; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 45 Summary of efficacy for 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		
Study identifier	Protocol Number: MK-1654-004 EudraCT: 2020-002405-26 EU CT: 2022-500350-42-00	
Design	Multicenter, efficacy, safety, parallel assignment, double-blind, placebo-controlled intervention	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Season 1: 365 days postdose Season 2: 515 days postdose not applicable not applicable
Hypothesis	Superiority	
Intervention groups	MK-1654	Single IM dose of clesrovimab on Day 1 Randomized N=2421
	Placebo	Single IM dose of placebo on Day 1 Randomized N=1211
Endpoints and definitions	Primary endpoint: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose	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
	Secondary endpoint: RSV-associated hospitalization	The efficacy of MK-1654 compared to placebo as assessed by the incidence of

	from Days 1 through 150 postdose	RSV-associated hospitalization from Days 1 through 150 postdose	
	Secondary endpoint: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose	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	
	Exploratory endpoint: RSV-associated severe MALRI from Days 1 through 150	The efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated severe MALRI (outpatient and inpatient) from Days 1 through 150 postdose	
Data cutoff date	04-MAR-2024		
Results and Analysis			
Analysis population	FAS population: all randomized participants who received 1 dose of study intervention.		
Analysis Description	**Primary Analysis: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose**		
Descriptive statistics and estimate variability	Intervention groups	MK-1654	Placebo
	Number of participants	n=2398	n=1201
	Participants with events n (%)	60 (2.5)	74 (6.2)
Effect estimate per comparison	Estimated efficacy (95% CI)	60.4 (44.1, 71.9)	
	Lower bound of 95% CI	>25%	
	One-sided p-value	p<0.001	
Analysis Description	**Secondary Analysis: RSV-associated hospitalization from Days 1 through 150 postdose**		
Descriptive statistics and estimate variability	Intervention groups	MK-1654	Placebo
	Number of participants	n=2398	n=1201
	Participants with events n (%)	9 (0.4)	28 (2.3)
Effect estimate per comparison	Estimated efficacy (95% CI)	84.2 (66.6, 92.6)	
	Lower bound of 95% CI	>0%	
	One-sided p-value	p<0.001	
Analysis Description	**Secondary Analysis: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose**		
Descriptive statistics and estimate variability	Intervention groups	MK-1654	Placebo
	Number of participants	n=2398	n=1201
	Participants with events n (%)	64 (2.7)	77 (6.4)
Effect estimate per comparison	Observed Efficacy (95% CI)	59.5 (43.3, 71.1)	
Analysis Description	**Exploratory Analysis: RSV-associated severe MALRI from Days 1 through 150 postdose**		

Descriptive statistics and estimate variability	Intervention groups	MK-1654	Placebo
	Number of participants	n=2398	n=1201
	Participants with events n (%)	2 (0.1)	12 (1.0)
Effect estimate per comparison	Observed Efficacy (95% CI)	91.7 (62.9, 98.1)	

Table 46. Summary of efficacy for 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		
Study identifier	Protocol Number: MK-1654-007 EudraCT: 2020-005996-11 EU CT: 2022-500752-39-00	
Design	Multicenter; efficacy; safety; parallel assignment; double-blind with in-house blinding (Part 1) and unblinded, open-label (Part 2); active control	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Participants in 1 RSV Season: 365 days post Dose 1 in RSV Season 1 Participants in 2 RSV Seasons: 180 days post RSV Season 2 dose not applicable not applicable
Hypothesis	No hypothesis testing associated with the objectives.	
Intervention groups	MK-1654	RSV Season 1: Single IM 105 mg dose of clesrovimab at Dose 1 (Day 1) followed by placebo at Dose 2 (Day 28), then unblinded at Day 60 Randomized N=450
		RSV Season 2: Single IM 210 mg dose of clesrovimab on Day 1 of RSV Season 2 Dosed N=60
	Palivizumab	RSV Season 1: Single IM dose of palivizumab at Dose 1 (Day 1) and Dose 2 (Day 28). Upon unblinding at Day 60, participants received at least 1 and up to 3 additional doses of palivizumab every 28 days. Randomized N=451
		RSV Season 2: Single IM 210 mg dose of clesrovimab on Day 1 of RSV Season 2 Dosed N=57

Endpoints and definitions	Secondary endpoint: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 post Dose 1 in RSV Season 1	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 post Dose 1		
	Secondary endpoint: RSV-associated hospitalization from Days 1 through 150 post Dose 1 in RSV Season 1	The incidence of RSV-associated hospitalization from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups		
Data cutoff date	05-FEB-2024 for participants randomized by 21-DEC-2023			
Results and Analysis				
Analysis population	FAS population: all randomized participants who received at least 1 dose of study intervention.			
Analysis Description	**Secondary Analysis: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 post Dose 1 in RSV Season 1**			
Descriptive statistics and estimate variability	Intervention groups	MK-1654	Palivizumab	
	Number of participants	n=443	n=437	
	Participants with events n (%)		14 (3.2)	12 (2.8)
Effect estimate per comparison	Observed efficacy (95% CI)	-18.0% (-155.5%, 45.5%)		
	Incidence rate (95% CI)	0.036 (0.020, 0.060)	0.030 (0.016, 0.053)	
Analysis Description	**Secondary Analysis: RSV-associated hospitalization from Days 1 through 150 post Dose 1 in RSV Season 1**			
Descriptive statistics and estimate variability	Intervention groups	MK-1654	palivizumab	
	Number of participants	n=443	n=437	
	Participants with events n (%)		5 (1.1)	6 (1.4)
Effect estimate per comparison	Incidence rate (95% CI)	0.013 (0.004, 0.030)	0.015 (0.006, 0.033)	

2.6.5.4. Clinical studies in special populations

Not applicable as the indication concerns neonates and infants below 1 year of age.

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Clesrovimab Recipients by Age of Dosing and Gestational Age

Table 47. Clesrovimab recipients by age of dosing and gestational age

	Number of participants																		
Gestational age at birth (weeks)[a]/Age at dosing (months)	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	Total
MK1654-004																				
≤1	0	0	0	0	0	1	1	5	16	36	14	23	31	60	78	72	30	10	0	377
>1 to ≤2	0	0	0	0	0	4	4	16	16	42	21	25	39	66	78	57	42	4	2	416
>2 to ≤3	0	0	0	0	4	6	5	11	10	19	21	22	23	69	80	85	42	12	0	409
Total (≤3 months)	0	0	0	0	4	11	10	32	42	97	56	70	93	195	236	214	114	26	2	1202
MK1654-007																				
≤1	0	0	0	0	0	1	1	5	15	21	12	0	1	2	1	1	0	1	0	61
>1 to ≤2	0	0	0	1	6	12	10	28	16	15	10	0	1	1	2	1	2	0	0	105
>2 to ≤3	1	3	2	10	12	6	12	12	8	9	5	1	0	2	1	2	0	0	0	86
Total (≤3 months)	1	3	2	11	18	19	23	45	39	45	27	1	2	5	4	4	2	1	0	252

[a]Gestational age categories are mutually exclusive and include gestational ages greater than the previous value and less than or equal to the current value.
For example, the column with gestational age of 26 weeks represents participants with gestational age >25 and ≤26 weeks.

GENOTYPIC AND PHENOTYPIC ANALYSIS OF RSV SAMPLES FROM CLESROVIMAB CLINICAL TRIALS MK-1654-004 AND MK-1653-007

In both MK-1654-004 and MK-1654-007, all RSV isolates detected in NP swabs had their entire F protein coding region sequenced and variants carrying substitutions in the clesrovimab binding site, Site IV, were prioritized for phenotypic testing.

The following analyses have been conducted:

- Analysis of amino acid substitutions affecting Site IV of the RSV F protein
- Analysis of clesrovimab epitope contact and adjacent residues
- Analysis of individual amino acid substitutions across the entire RSV F protein
- Analysis of concurrent amino acid substitutions across the entire RSV F protein
- Analysis of F protein substitutions that became dominant in recent years

Genotypic Analysis of RSV F Gene in MK-1654-004 and MK-1654-007 Studies

The full-length F gene from RSV positive NP swabs was assessed by NGS methods. For MK-1654-004, a total of 568 samples [319 (clesrovimab arm) + 249 (placebo arm) from 307 and 226 participants, respectively] were successfully analyzed. As the MK-1654-007 is an ongoing study, a total of 65 samples [33 (clesrovimab arm) + 32 (placebo/palivizumab arms) from 29 and 28 participants, respectively] were successfully analyzed as of the cutoff date of February 5th, 2024, for the interim analysis. The resulting RSV F nucleotide sequences were translated into amino acid sequences and aligned against reference sequences. Amino acid substitutions compared with the reference sequences were determined for the full-length F protein (AA 1 to 574), including the clesrovimab binding epitope, Site IV (AA 426 to 447).

Substitutions occurring in the clesrovimab binding site were prioritized to identify variants with higher likelihood for altered susceptibility to clesrovimab for phenotypic analysis.

The majority of F protein Site IV substitutions detected in RSV-A or RSV-B viruses within the clesrovimab treatment group affected the G446 residue, which was changed to either E, R or W. The G446E/R/W Site IV substitutions were detected in 11 participants across the MK-1654-004 and MK-1654-007 studies. The G446E substitution was previously detected in 3 of 15,527 RSV F protein sequences (0.02%) reported in the GenBank database. The same G446E substitution was also identified in a previous RSV-A MARM study. It resulted in complete loss of binding to clesrovimab; however, this variant was also shown to have reduced viral fitness in vitro as compared to the WT RSV-A strain.

In the MK-1654-004 study, among the 7 participants who had G446E/R/W substitutions, there were no cases of RSV-associated MALRI, and 1 case of RSV-associated hospitalization.

G446 variants were observed in samples from 4 MK-1654-007 participants. Only 2 cases of RSV-associated MALRI were detected in the MK-1654-007 study, and both carried a G446R substitution:

- During RSV Season 1 (Days 1 to 180 postdose), a participant with RSV encoding Site IV substitution (G446R) met the criteria for RSV-associated severe MALRI. This participant was hospitalized for this event. This infant had an underlying comorbidity of congenital heart disease. The RSV positive study sample was obtained on Day 13 post Dose 1 in RSV Season 1.
- During RSV Season 2, another participant, who was dosed with clesrovimab in both Seasons 1 and 2 with a Site IV substitution (G446R) met the criteria for RSV-associated MALRI. This participant's underlying comorbidity was congenital heart disease requiring surgical correction. This infant did not require hospitalization, and symptoms resolved with outpatient supportive care. The RSV positive study sample was obtained on Day 8 post Dose 2 in RSV Season 2.

In addition to the G446 substitutions described above, the following Site IV substitutions were identified in MK-1654-004 participants, and none were associated with RSV-associated MALRI:

- An RSV-B variant encoding I432V Site IV substitution was detected in a participant on Day 362 postdose. Previously, the I432T variant was identified in 5 RSV-A and 1 RSV-B samples (0.04 %) in the GenBank database. The I432T substitution was shown to reduce clesrovimab neutralization efficiency of RSV-A by 3.7-fold and RSV-B by 1.6-fold. However, the I432T variant was outcompeted by the WT virus in in vitro growth competition assays, suggesting that it might have lower fitness.
- An RSV-A variant encoding S436F Site IV substitution was detected in a participant on Day 459 postdose. While residue 436 is a part of site IV, it is not thought to interact directly with clesrovimab as it is more than 5 angstroms (Å) away from the closest known contact between clesrovimab and RSV F protein based on X-ray crystallography structure.
- An RSV-A variant encoding D440G Site IV substitution was found in a participant at Day 429 postdose and is currently being evaluated using reverse genetics systems for phenotyping purposes.
- An RSV-A variant encoding K433T Site IV substitution was only detected in 1 participant in the placebo group and had a low variant allele frequency (21.5%).

Table 48. Clesrovimab epitope substitutions together with any associated virus phenotype observed in cell culture, GenBank or MK-1654-004/MK-1654-007 clinical studies

AA Position #	AA Substitution	Cell culture			GenBank[a]			Clinical trials[b]		
		RSV-A	RSV-B	Virus Phenotype	RSV-A	RSV-B	Virus Phenotype	RSV-A	RSV- B	Virus Phenotype
N426	N426T	None	None	NA	1	1	ND	0	0	NA
K427	None	None	None	NA	0	0	NA	0	0	NA
N428	N428D	None	None	NA	1	0	ND	0	0	NA
R429	None	None	None	NA	0	0	NA	0	0	NA
I432	I432V	None	None	NA	1	0	ND	0	1	ND
	I432T	None	None	NA	5	1	Neutralization potency: 4X less for RSV-A and 2X less for RSV-B	0	0	NA
K433	K433Q	None	None	NA	0	1	ND	0	0	NA
	K433R	None	None	NA	0	4	ND	0	0	NA
	K433T	None	None	NA	0	0	NA	1	0	ND
D440	D440N	None	None	NA	0	2	ND	0	0	NA
	D440G	None	None	NA	0	0	NA	1	0	TBD
Y441	None	None	None	NA	0	0	NA	0	0	NA
S443	S443T	None	None	NA	2	1	ND	0	0	NA
	S443P	1	1	Loss of neutralization for RSV-A and RSV-B	0	0	NA	0	0	NA
	S443P + K445N	1	None	Loss of neutralization for RSV-A	0	0	NA	0	0	NA
	S443P + G446E	1	None	Loss of neutralization for RSV-A	0	0	NA	0	0	NA
K445	K445R	None	None	NA	3	1	Neutralization potency: 5X less for RSV-B[c]	0	0	NA
	K445N + S443P	1	None	Loss of neutralization for RSV-A	0	0	NA	0	0	NA
G446	G446V	None	None	NA	0	1	ND	0	0	NA
	G446E	1	None	Loss of neutralization for RSV-A	3	0	ND	1	2	TBD
	G446E + S443P	1	None	Loss of neutralization for RSV-A	0	0	NA	0	0	NA
	G446R	None	None	NA	0	0	NA	2	2	TBD
	G446W	None	None	NA	0	0	NA	2	0	TBD

AA Position #	AA Substitution	Cell culture			GenBank[a]			Clinical trials[b]		
		RSV-A	RSV-B	Virus Phenotype	RSV-A	RSV-B	Virus Phenotype	RSV-A	RSV- B	Virus Phenotype
V447	V447M	None	None	NA	3	0	ND	0	0	NA
	V447L	None	None	NA	0	1	ND	0	0	NA

[a] Total GenBank sequences analyzed = 15,527
[b] Substitutions detected in the clesrovimab epitope for both clesrovimab and control arms
[c] The K445R substitution was observed in an RSV-B isolate (B-HMC-22), which was among the panel of 47 clinical isolates tested in neutralization assays [Ref. 4.2.1.1: PD004MK1654].
ND=Not determined; NA=not applicable; TBD=To be determined
n = number of isolates, sequences (GenBank) or participants (clinical trials)

Conclusion

- Across the MK-1654-004 and MK-1654-007 studies, a total of 633 RSV positive NP swabs were successfully analyzed. RSV isolates in those swabs had their entire F protein coding region sequenced and variants carrying F protein substitutions (as compared to the reference strains) were reported.
- The G446E/R/W substitution was observed with allele frequencies of ≥10% in 11 participants who received clesrovimab across both studies, 2 of whom met the criteria of RSV-associated MALRI. Both cases were reported in the MK-1654-007 study, which enrolled high-risk patients with other comorbidities. The first participant was hospitalized with severe RSV-associated MALRI in RSV Season 1, while the second one had RSV-associated MALRI in RSV Season 2. Seven participants from MK-1654-004 had similar mutations at the G446 position but did not register as cases of RSV-associated MALRI. In the MK-1654-004 study, among the 7 participants who had G446E/R/W substitutions, there were no cases of RSV-associated MALRI and 1 case of RSV-associated hospitalization.
- No F protein individual substitution or a set of concurrent substitutions were associated with clesrovimab-treated participants as compared to the control arms.
- Among F protein amino acid residues that are ≤5 Å away from the clesrovimab binding epitope, only K470R was observed in 1 clesrovimab-treated participant in the MK-1654-004 study who did not meet the criteria for RSV-associated MALRI or hospitalization.
- The majority of F protein substitutions with prevalence of ≥50% were observed in contemporary RSV strains (isolated between December 2016 and July 2021) that were potently neutralized by clesrovimab.

2.6.5.7. Supportive study(ies)

Association between anti-drug antibodies and efficacy endpoints

Study MK-1654-004

The proportions of participants in the MK-1654 group who were ADA positive were low at Day 150 (5.7%) and through Day 240 (12.0%). Per protocol, ADA was first measured at Day 150, after almost all efficacy cases had been observed, and so it was not possible to determine the timing of ADA development relative to the timing of developing RSV-associated MALRI or hospitalization.

Table 49. Summary of RSV-associated Outpatient and Inpatient MALRI by ADA Status at Day 150 in participants treated with MK-1654 105 mg Days 1 to 150 postdose (full analysis set)

	ADA Negative				Non-Treatment Emergent ADA Positive				ADA Positive[a]			
Endpoint	n	Number of Cases	Total Follow-up Time in Months[b]	Incidence Rate Over 5 Months (95% CI)[c]	n	Number of Cases	Total Follow-up Time in Months[b]	Incidence Rate Over 5 Months (95% CI)[c]	n	Number of Cases	Total Follow-up Time in Months[b]	Incidence Rate Over 5 Months (95% CI)[c]
RSV-associated Outpatient and Inpatient MALRI	1898	41	9340.0	0.022 (0.016, 0.030)	50	0	250.0	0.000 (0.000, 0.074)	120	14	560.7	0.125 (0.068, 0.209)
By RSV Type												
RSV A	1898	22	9401.7	0.012 (0.007, 0.018)	50	0	250.0	0.000 (0.000, 0.074)	120	5	583.7	0.043 (0.014, 0.100)
RSV B	1898	21	9419.6	0.011 (0.007, 0.017)	50	0	250.0	0.000 (0.000, 0.074)	120	9	577.0	0.078 (0.036, 0.148)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] The ADA positive population includes treatment emergent ADA positive participants and treatment boosted ADA positive participants.
[b] One month is defined as 30 days for the total follow-up time calculation.
[c] Five months is defined as 150 days. 95% CI of incidence rate is estimated by exact Poisson confidence limits.
n=Number of participants randomized and dosed with MK-1654 105 mg and eligible for inclusion in the full analysis set population in the given ADA category.
ADA=anti-drug antibody; CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P004V01MK1654: adam-adsl; adeff]

Study MK-1654-007

The proportions of participants in the MK-1654 group who were ADA positive were low at Day 150 (4.5%) and through Day 240 (13.0%) in RSV Season 1. As per the protocol, ADA was first measured at Day 150, after almost all efficacy cases had been observed, and it was therefore not possible to determine the timing of ADA development relative to the timing of developing RSV-associated MALRI or hospitalization.

Table 50. Summary of RSV-associated Outpatient and Inpatient MALRI by ADA Status at Day 150 in RSV Season 1 in participants treated with MK-1654 105 mg Days 1 to 150 postdose (full analysis set)

	ADA Negative				Non-Treatment Emergent ADA Positive				ADA Positive[a]			
Endpoint	n	Number of Cases	Total Follow-up Time in Months[b]	Incidence Rate Over 5 Months (95% CI)[c]	n	Number of Cases	Total Follow-up Time in Months[b]	Incidence Rate Over 5 Months (95% CI)[c]	n	Number of Cases	Total Follow-up Time in Months[b]	Incidence Rate Over 5 Months (95% CI)[c]
RSV-associated Outpatient and Inpatient MALRI	273	8	1342.8	0.030 (0.013, 0.059)	4	0	20.0	0.000 (0.000, 0.922)	13	3	58.6	0.256 (0.053, 0.748)
By RSV Type												
RSV A	273	3	1353.9	0.011 (0.002, 0.032)	4	0	20.0	0.000 (0.000, 0.922)	13	2	63.3	0.158 (0.019, 0.570)
RSV B	273	5	1353.1	0.018 (0.006, 0.043)	4	0	20.0	0.000 (0.000, 0.922)	13	1	60.3	0.083 (0.002, 0.462)

Every participant is counted a single time for each applicable endpoint category. A participant may appear in more than one endpoint category. For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis.
[a] The ADA positive population includes treatment emergent ADA positive participants and treatment boosted ADA positive participants.
[b] One month is defined as 30 days for the total follow-up time calculation.
[c] Five months is defined as 150 days. 95% CI of incidence rate is estimated by exact Poisson confidence limits.
n=Number of participants randomized and dosed with MK-1654 105 mg and eligible for inclusion in the full analysis set population in the given ADA category.
ADA=anti-drug antibody; CI=Confidence interval; MALRI=Medically attended lower respiratory infection; RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adeff]

2.6.6. Discussion on clinical efficacy

The clinical development program consists of 6 clinical studies out of which 4 were conducted in infants. The **pivotal evidence** for the sought after indication is derived from 2 ongoing clinical studies which enrolled healthy full-term (gestational age ≥35 weeks) and preterm (gestational age ≥29 weeks to <35 weeks) infants (**MK-1654-004**) and infants with increased risk for severe RSV disease due to prematurity (born at ≤35 weeks gestational age), congenital heart disease (CHD) or chronic lung disease (CLD) (**MK-1654-007**). Clinical studies were considered compliant with the PIP by the PDCO (EMA/PE/0000224244). Overall, the clinical development plan is in principle considered appropriate to inform about efficacy and safety in the proposed indication and target population. Efficacy endpoints in study **MK-1654-007** (high risk infants) were evaluated as secondary objective(s) without hypothesis

testing and thus, the study was not powered to demonstrate noninferiority for efficacy of clesrovimab compared with palivizumab. Instead, efficacy is inferred by extrapolation from healthy preterm and full-term infants (Study MK-1654-004) to the high risk population based on PK bridging. The lack of a formal relative efficacy study in comparison to palivizumab for eligible infants is acceptable due to feasibility issues. Such an approach was in principle agreed on in a scientific advice procedure (EMA/CHMP/SAWP/340668/2019). The same strategy was also employed in the development program for nirsevimab (Beyfortus, EMEA/H/C/005304/0000).

Dose selection

Based on modelling results from Study MK-1654-002 data, suggesting that efficacy against RSV plateaus between doses of 90 to 105 mg, a flat 105-mg IM dose was selected for all preterm and full-term infants born during or entering their first RSV season (please refer further to the Clinical Pharmacology section).

A recommendation to administer an additional 105 mg clesrovimab dose for infants undergoing cardiac surgery with cardiopulmonary bypass during the RSV season has been put forward by the Applicant.

Design and conduct of clinical studies

For both main studies, enrolment was to commence 4 weeks prior the estimated onset of the RSV season and was to end before the estimated peak of the RSV season. Infants being born outside the RSV season, MK-1654 should be administered once prior to the start of their first RSV season. The timing of dosing in the studies is not clearly specified, but it is mentioned that it is assisted by epidemiological monitoring and would also be based on the normal pattern of RSV seasons. However, the study was initiated during the Covid-19 pandemic where RSV seasonality was disrupted. Upon request, a descriptive analysis on the proportion of participants dosed relative to the RSV season was provided (based on publicly available retrospective RSV surveillance data for the years the studies were conducted [2021-2024]). Seemingly roughly half of participants enrolled in temperate regions were dosed after the RSV season peak. This is seen suboptimal from an efficacy perspective. However, the challenges of RSV seasonality disruption during the Covid-19 pandemic are acknowledged and notwithstanding, a sufficient number of cases accrued for efficacy analyses conducted in Study MK-1654-004. In addition, the timing of dosing relative to the RSV season was balanced between treatment arms and included all scenarios (dosing prior season start, and within the season). Therefore, no concern as regards efficacy outcomes arise and the dosing recommendation in section 4.2 of the SmPC is acceptable.

For both main studies, no estimand was defined in either the protocol or SAP. This mainly concerns handling of missing data and exclusion of subjects from the primary analysis set (FAS). As regards the statistical methods, the modified Poisson model used to estimate efficacy is generally endorsed. To investigate the robustness of the results with respect to assumptions on seasonality with respect to the actually chosen observation time in relation to real timing of the RSV season a sensitivity analysis in the form of a Cox model, that does not make this assumption was requested. The estimated efficacy was consistent with the estimates from the primary analysis. In addition, missing data was not imputed. A tipping point analysis to assess the robustness of the results with respect to deviations from the missing at random assumption was requested for both studies. A less conservative sensitivity analysis using a reference-based imputation approach was conducted. The provided analysis did not cover the most conservative assumptions of the requested tipping-point analysis but only the case where the event rate for subjects who are lost to follow-up is assumed to be equal to the event rate of observed subjects in the placebo arm. This is still slightly more conservative than the main analysis which assumed missingness at random. In light of the good agreement between the provided

sensitivity analysis and the primary analysis as well as the low rate of missing observations, the issue was nevertheless considered resolved.

Notably, the dose formulation in both main studies was a vial while the final drug product will be a pre-filled syringe but analytical comparability between drug product manufactured in vial and pre-filled syringe presentation was sufficiently demonstrated at the quality level.

Study MK-1654-004

Study MK-1654-004 was a double-blind, randomized, placebo-controlled Phase 2b/3 study. The study was conducted across 22 countries in the northern and southern hemisphere. The overall study design is considered appropriate.

Healthy male and female infants who had a chronological age from birth up to 1 year (Phase 2b cohort: from >2 weeks of age up to 1 year) and entering their first RSV season at the time of consent were enrolled in this study. Inclusion and exclusion criteria are well defined and overall acceptable. Approximately 3300 participants were planned to be enrolled and participants were randomized 2:1 to MK-1654 or placebo, which is acceptable.

Two pre-defined interim analyses (IA) were conducted by an external unblinded statistician and reviewed by eDMC. After completion of the Day 42 visit of the Phase 2b cohort the first interim analysis was performed, while screening and randomization was continued. The second IA comprised a futility evaluation after 40 RSV-associated MALRI cases accrued in total (i.e. MK-1654 and placebo arms). No concern arises thereof and pooling of efficacy data from the Phase 2b cohort and Phase 3 cohort is thus, acceptable.

Study assessments to evaluate efficacy endpoints based on respiratory infection assessments are considered appropriate to capture as many cases as possible. Trigger symptoms to arrange a respiratory assessment visit were pre-specified in the protocol and are acceptable. The respiratory infection assessment visit was to be arranged ideally within 3 days upon symptom onset or worsening but could be performed within 12 days, which is considered rather long and may result in false negative cases due to cessation of viral shedding at the time of NP sample taking. Hence, a maximum of 7 days was recommended during the scientific advice procedure (EMA/CHMP/SAWP/340668/2019) and an overview on how many participants had a NP sample taken within 3 to 7 days from symptom onset/worsening and for how many an extended time window was necessary was requested. The majority of study swabs (>~85%) were collected within 7 days in both main studies, and importantly, no major difference as regards sampling window is apparent between treatment arms. The Applicant's argumentation justifying the 12-day window including the sensitivity of RT-PCR methodology to confirm RSV positivity and the reported longer duration of viral shedding in the evaluated infant population is considered plausible. Therefore, a meaningful impact on efficacy conclusions due to the 12-day sampling window is deemed unlikely. Case ascertainment rested on laboratory diagnostics via RT-PCR and examinations (ideally) conducted by the investigator or medical designee during a respiratory assessment visit. No external adjudication committee confirming case ascertainment was seemingly in place though, which would have been desirable. However, the planned procedures for respiratory infection assessment and case ascertainment appear overall appropriate.

The primary efficacy objective is considered clinically relevant. The primary efficacy endpoint, number of participants with RSV-associated MALRI from Days 1 through 150 postdose, reflects the primary study objective and the intended indication. The endpoint is clinically relevant, reproduceable in a clinical setting and in line with endpoints used in studies on similar products. The required criteria for an RSV-associated MALRI encompass indicators of LRT involvement (wheezing, chest wall indrawing/retraction, rales/crackles) and severity (hypoxemia, tachypnoea, dehydration) out of which one had to be met in addition to the presence of cough or difficulty in breathing and an RSV-positive

RT-PCR from a NP swab sample. The primary definition is broad and likely captures cases with a differing degree in severity, which is acceptable. Upon request, a descriptive comparison of the different lower respiratory symptoms/indicators considered for RSV-associated MALRI and severe MALRI case ascertainment between treatment arms was provided (see below).

One of the secondary objectives, RSV-associated hospitalisation, is of interest but the interpretability of outcomes is not straight forward due to local differences in admission rates. Therefore, it is not considered a sensitive measure to evaluate disease severity. Furthermore, based on the endpoint definition of RSV-associated hospitalisation in this study (Hospital admission for respiratory illness AND RSV-positive RT-PCR NP sample), it is unclear if qualified cases had a positive RSV RT-PCR test prior hospitalisation or whether RSV was acquired just in the hospital. In addition, no lower respiratory tract infection had to be confirmed for this endpoint to be met. Evaluation of disease severity, that could or could not lead to hospitalisation, is considered a relevant outcome though, and the need to be assessed as an important secondary endpoint was stated in a previous scientific advice (EMA/CHMP/SAWP/713315/2017). However, to estimate the efficacy of MK-1654 by the incidence of RSV-associated severe MALRI was included here only as pre-specified exploratory objective.

A total of 3632 participants have been randomized and the study is still ongoing. However, all included participants that did not discontinue completed either study Day 240 (RSV Season 1) or Day 515 (RSV Season 2). Thus, all enrolled participants completed the study period relevant for efficacy assessments (Day 150 and Day 180). The to date completion rate was high as less than 7% of participants discontinued in both treatment groups and reasons for discontinuation were comparable between study arms.

The primary efficacy analysis was based on the FAS population, which included roughly 99% of all participants. Exclusions from the FAS were not entirely aligned with the pre-specified FAS population but outlined reasons can be followed and the overall number of exclusions from the FAS is low. Supportive efficacy analyses were performed on the per-protocol (PP) population, which included 98.8% and 99.0% of participants randomised to the MK-1654 arm and placebo arm, respectively. Reasons for exclusions appear overall balanced and are not concerning. The proportion of participants with important protocol deviations was balanced between the MK-1654 and placebo groups (13.2% and 15.8%, respectively). The most frequently reported clinically important protocol deviation was non-sampling of the required study NP swab per protocol from participants with respiratory infection symptoms. However, the proportion of respiratory infection events with at least 1 NP swab result within the analysis window was high and balanced between both arm (96.4% in the MK-1654 group and 94.3% in the placebo group).

Investigator site audits were performed at 10 sites. Two episodes of site-specific GCP non-compliance were described at 3 different sites. One episode entailed premature unblinding (3 participants) due to safety reasons. This unblinding was not inadvertent. At one site premature unblinding (5 patients) could not be ruled out.

Study MK-1654-007

Study MK-1654-007 is a phase 3, partially blinded, randomized, palivizumab-controlled Phase 3 study. The study is conducted across 27 countries and approximately 1000 participants are planned to be enrolled. The overall study design is considered adequate. Palivizumab as comparator is relevant and adequate, with a similar patient population and indication. Notably, the study was conducted double-blind up to the Day 60 visit and was open-label for the remaining time. This can overall be followed as additional placebo injections for the at risk infants in the MK-1654 arm are sparred. As efficacy is demonstrated by a PK bridging strategy via extrapolation from Study MK-1654-004, no concern arises as regards the PK data. However, a concern remained for secondary study outcomes resting on case ascertainment after unblinding. Upon request, the Applicant provided the number of cases for each

secondary efficacy endpoint, which was roughly balanced between the double blind and open-label period as well as between study arms.

For RSV Season 1, the planned study population encompassed infants recommended to receive palivizumab and being either born ≤35 weeks of gestation (early and moderate preterm) without having CLD and hemodynamically significant CHD, or having CLD of prematurity, or hemodynamically significant CHD. No concern with respect to the inclusion and exclusion criteria arises. Approximately 1000 participants are planned to be enrolled and participants were randomised 1:1 to MK- 1654 and palivizumab, which is acceptable.

Study assessments to evaluate efficacy endpoints were largely comparable to procedures outlined in Study MK-1654-004.

Efficacy was evaluated as secondary outcome. Furthermore, no hypothesis testing was foreseen. This is acceptable as discussed above. The pre-defined RSV-associated MALRI case definition aligns with that from Study MK-1654-004, which is endorsed, while the same trade-offs for hospitalisation endpoints apply (see above for Study MK-1654-004).

The study is still ongoing and up to the data cut-off of this interim CSR (05 February 2024), 901 participants have been randomised and 707 participants (78.9%) had completed the RSV Season 1 Day 150 visit. The up to date discontinuation is considered low (7.8% [35/450 participants] in the MK-1654 group and 6.9% [31/451 participants] in the palivizumab group). Upon request, updated efficacy data were provided with a data cut-off of 26 September 2024 and included 52 additional participants dosed with MK-1654 and 49 additional participants dosed with palivizumab. The provided data are overall consistent with conclusions drawn from data submitted at the initial submission (data cut-off 05 February 2024).

The majority of participants were included in the FAS population, which encompassed 98.4% of participants in the MK-1654 group and 96.9% in the palivizumab group. While exclusions from the FAS were not entirely aligned with the pre-specified FAS population, outlined reasons can be followed and the overall number of exclusions is low. Supportive efficacy analyses were performed on the per-protocol (PP) population, which included 97.8% and 81.4% of participants randomised to the MK-1654 arm and palivizumab arm, respectively. The observed imbalance in exclusion is due to protocol deviation linked to palivizumab dosing as discussed below.

Overall, the proportion of participants with a protocol deviation appears high, which may be linked to the study population. A roughly 2-fold higher proportion of participants in the palivizumab group had important protocol deviations compared to the MK-1654 group (47.0% and 23.3%, respectively). This observation is predominantly driven by a higher occurrence of deviations related to study interventions (2.0% MK-1654 arm, 31.0% palivizumab arm), linked to an out of allowable window administration of palivizumab (32 days from previous dose), which was reported for 109 participants (24.2%) in the palivizumab arm and for 36 participants (8.0%) these deviations were judged as clinically important. In addition, 16 participants in the palivizumab arm (3.5%) received an incorrect number of doses (or dose volume). An overall impact on comparative secondary efficacy outcomes, albeit not of confirmatory nature, cannot be excluded. Notably, PP analyses excluded participants with incorrect number of doses or that received less than three palivizumab doses and above mentioned 36 participants with dose delays, while overall 109 participants had out of window palivizumab dosing. The extended window of 37 days for palivizumab dosing, with respect to the previous dose, used to consider the PP population in this regard is not further justified. While these deviations are not optimal, no concern is raised as the study is not powered to demonstrate comparable efficacy of MK-1654 and palivizumab. With the overall low number of cases that were reported, drawing robust conclusions is impeded. In addition, as regards important protocol deviations, non-sampling of the required study NP swab per protocol from participants with respiratory infection symptoms, the proportion of events with

at least 1 NP swab result within the analysis window was high and balanced between both arms (93.9% in the MK-1654 group and 93.4% in the palivizumab group).

Efficacy data and additional analyses

For both Study MK-1654-004 (healthy infants) and Study MK-1654-007 (at risk infants), demographics and baseline data were overall balanced between treatment groups. The enrolled participants are deemed representative for intended population, with unclarities outlined further below. It is emphasized that the inclusion criteria and thus the indication is purely based on the child's age including GA. As regards healthy infants, the anticipated minimum number of moderate preterm infants (≥29 weeks and <35 weeks of GA) were enrolled (minimum number of at least 600 infants) out of which 422 were dosed with MK-1654. The number of very premature infants (GA <29 weeks, non CLD, non CHD) treated with MK-1654 is limited (n=26), while in total 98 participants with a GA <29 weeks (independent of CLD/CHD) were included among MK-1654-treated participants, with a minimum GA of 23.6 weeks. Furthermore, based on the lower end of the represented weight range (see below), it appeared plausible to conclude that (very) early preterm infants were not dosed early in life. Upon request, the Applicant provided cross-tabulated data on study participants by age of dosing and gestational age. Among infants with ≤29 weeks GA, 39 were dosed within 3 months after birth, 32 between >2 to ≤3 month after birth, 7 between >1 to ≤2 month after birth and none within ≤1 month after birth. For infants with <29 weeks gestational age, 17 and 1 received MK-1654 within their first 3 and 2 month of life, respectively. No participant ≤25 weeks GA was dosed within first 2 months of life The limited available data in this subpopulation is reflected in the SmPC section 4.2, which is considered appropriate.

In Study MK-1654-004, roughly 68% of participants were enrolled in the northern hemisphere and the majority was from a temperate region (80.9%), which was similar in Study MK-1654-007. The median age for healthy infants was 3 months and 2.5 months for at risk infants, with roughly 80% and 89% of the study population representing infants ≤6 months of age, respectively. As regards the included weight range, infants with a wide weight range at randomization were included (1.6 to 11.9 kg healthy infants, 1.1 to 9.6 kg at risk infants). It is acknowledged that not the entire weight range of the target population can be represented in clinical trials and a respective statement in the SmPC was added. As regards at risk infants, the participants conditions linked with an increased risk for RSV disease were generally comparable between treatment arms and the representation of conditions linked to CHD/ CLD is acceptable. Overall, 250 participants (27.9%) had CLD, 101 participants (11.3%) had CHD, 50 participants (5.6%) had a GA less than 29 weeks (without CLD or CHD), and 495 participants (55.2%) had a GA greater than or equal to 29 weeks (without CLD or CHD).

Non-investigative vaccines and immunoglobulin products were allowed, and their usage was overall balanced between the treatment arms.

Study MK-1654-004

Primary efficacy endpoint

The **RSV-associated MALRI** from Day 1 through **Day 150 postdose** case definition was met in 60/2398 participants in the MK-1654 group and in 74/1201 participants in the placebo group in the FAS population, reflected by an observed incidence rate of 0.026 vs 0.065, respectively. The estimate for efficacy (95% CI) of MK-1654 relative to placebo was 60.4% (44.1%, 71.9%). The primary study objective has been met as the lower bound of the 95% CI was >25%. Corresponding Kaplan-Meier curves of time from dosing until first RSV-associated MALRI demonstrated a clear separation between treatment arms over the entire primary surveillance period (Day 1 to 150 postdose). Notably, the majority of cases occurred prior to 90 days with respect to dosing in both treatment arms. The result

was consistent in the PP population and when RSV PCR results from both, study central and local laboratories were considered. Additional sensitivity analyses were requested and the estimated efficacy were in line with the estimates from the primary analysis (see above). Comparable results were obtained when a 180 day follow-up postdose was considered as secondary endpoint.

A descriptive analysis of signs/symptoms of RSV-associated MALRI cases was provided upon request. A similar proportion between treatment groups had cough (98.4% vs 98.7% MK-1654 vs placebo) and 12.5% vs 24.7% reported difficulty in breathing (MK-1654 vs placebo). As regards the LRTI indicator, a comparable percentage of cases presented with wheezing (54.7% MK-1654 vs 53.2% placebo) and rales/crackles (50.0% MK-1654 vs 46.8% placebo). Concerning the severity indicator, a numerically smaller proportion of infants in the MK-1654 group reported chest wall indrawing (14.1% MK-1654 vs 20.8% placebo) and hypoxemia (7.8% MK-1654 vs 15.6% placebo), while 31.3% vs 36.4% reported tachypnoea (MK-1654 vs placebo). This observation is in line with efficacy outcomes on severe RSV-associated MALRI (see below).

Regarding RSV-associated MALRI due to RSV A vs RSV B, the efficacy estimate (95% CI) trended lower for RSV A-associated MALRI with respect to RSV B-associated MALRI: 44.4% (5.5%, 67.3%) RSV A vs 66.2% (47.2%, 78.3%) RSV B. Overall, there were more cases due to RSV B, which was more apparent in the placebo group: 29 cases and 33 cases among 2398 participants due to RSV A vs RSV B, respectively, in the MK-1654 group; 26 cases and 48 cases among 1201 participants due to RSV A vs B, respectively, in the placebo group. Overall, the data indicate at least a numerical benefit for MK-1654 vs placebo in preventing MALRI due to RSV A and RSV B, respectively, but the lower number of cases due to RSV A decreases the precision of the estimate and the study was overall not powered to detect efficacy per RSV subtype.

Secondary efficacy endpoints

The RSV-associated **hospitalization** case definition was met in 9/2398 participants in the MK-1654 group and in 28/1201 participants in the placebo group, respectively, up to **Day 150** postdose. The estimate for efficacy (95% CI) of MK-1654 relative to placebo was 84.2% (66.6%, 92.6%). Thus, the statistical success criterion was met as the lower bound of the 95% CI was >0%. Although provided efficacy estimates on RSV-associated hospitalisation indicate a benefit, the interpretation of this endpoint is not straightforward and outcomes on this endpoint should be interpreted with afore-mentioned trade-offs (see above). Furthermore, no lower respiratory tract infection had to be confirmed for this endpoint to be met. This was addressed by an exploratory endpoint on LRI hospitalisation, the outcomes of which support above estimates.

As mentioned above, the incidence of RSV-associated **severe MALRI** is considered clinically relevant, which was an exploratory endpoint. The incidence of severe MALRI from Day 1 to Day 150 postdose was 0.001 (2/2398 cases) in the MK-1654 group and 0.010 (12/1201 cases) in the placebo group with an efficacy estimate (95% CI) of 91.7% (62.9%, 98.1%). Among severe RSV-associated MALRI cases, all reported with hypoxemia (3 severe cases in the placebo arm) and all but one case in the placebo group required oxygen support. Based on this, the severity of cases is agreeable.

Additional estimates on RSV-associated respiratory disease outcomes, evaluated as exploratory/tertiary endpoints, are consistent with primary analyses.

Exploratory Season 2 data on RSV-associated MALRI obtained from a subset of enrolled participants do not raise concerns pertaining to an increased disease susceptibility for Season 2 of infants treated with MK-1654 during their first season. Demographics of the population followed through their second RSV season are overall consistent with the full evaluated population in Study MK-1654-004.

Regarding the duration of protection, Day 150 postdose data were overall consistent with Day 180 postdose data indicative of a sustained effect through 6 months. However, roughly half of study

participants enrolled in temperate regions were dosed after the estimated RSV season peak and a small proportion prior to the RSV season start (see above). This hampers the assessment regarding the duration of protection claim due to a potentially decreased RSV exposure risk at later time points. In Study MK-1654-004, the majority of RSV-associated MALRI cases were reported prior to 90 days postdose and the incidence decreased from day 150 onwards in both study arms. A limited number of cases between Day 150 and 180 postdose occurred. Overall, supportive efficacy data have been provided but the claim regarding a 6-month duration of protection rests on a low case incidence during the respective time interval. Moreover, no SNA titer threshold is known to confer protection against RSV (see the Clinical Pharmacology section). These limitations are reflected in the SmPC.

Within the context of the single-dose regimen, subgroup analyses per age and weight are of special interest. MK-1654 exposure (AUC0-150d) was decreased in infants ≥5kg, which is a potential efficacy concern in relation to the non-weight-based dosing regimen. Efficacy estimates trended lower in infants with ≥5 kg at randomisation but differences are likely not meaningful. However, among age at randomization subgroups (≤2 weeks, <6 months and ≥6 months), there was a trend in decreased efficacy on RSV-associated MALRI with increasing age. The oldest cohort had an estimated efficacy of 19.5% (95% CI -101.3, 66.8%), while infants with <6 months of age and infants with ≤2 weeks of age had an estimated efficacy of 65.3% (95% CI 49.5, 76.4%) and 91.2% (95% CI 34.2%, 99.6%), respectively. The overall low number of cases in the youngest and oldest age subgroup with respect to infants <6 months of age is noted though, which impedes the interpretability of the data and the precision of efficacy estimates, as reflected by wide 95% CI. Age subgroup results for RSV-associated hospitalisation were inconclusive given the low number of cases in ≥6 months of age infants (2 cases vs 0 cases in the MK-1654 vs placebo group). The observed trend towards a decreased efficacy when infants are ≥6 months of age at dosing, along with an observed lower exposure, required further clarification within the context of the dosing regimen. The Applicant provided further efficacy data. Although efficacy estimates for some endpoints were lower in older and heavier infants, 95% CI widely overlapped. In addition, estimates across additional efficacy endpoints are consistent with trends from the overall population. Based on additional PK/PD data, it is not considered necessary to recommend a 210 mg dose in infants aged 6-12 months during Season 1 (please refer to the Clinical Pharmacology section).

The presented post-hoc analyses based on an alternative RSV-associated MALRI case definition support the beneficial effect of MK-1654 in the prevention of RSV-associated MALRI.

Study MK-1654-007

One of the secondary efficacy endpoints was the number of participants with **RSV-associated MALRI** (outpatient and inpatient) from Day 1 through **Day 150 postdose** in RSV Season 1. There were 14/443 and 12/437 participants meeting the pre-specified RSV-associated MALRI criteria in the MK-1654 group and the palivizumab group, respectively, in the FAS. This resulted in overall comparable incidence rates (0.036 MK-1654 group vs 0.030 palivizumab group) over 5 months. The efficacy estimate (95%) of -18.0 (-155.5%, 45.5%) indicates a trend in favour of palivizumab. The observed difference is driven by 2 cases and thus, is likely chance finding. Notably, almost 25% of participants in the palivizumab arm had a protocol deviation concerning palivizumab dosing out of which 8% were deemed clinically important and thus, were excluded from the PP analysis (as discussed above). It is however unclear whether any of the affected subjects, that were not excluded, met the RSV-associated MALRI criteria. The result in the PP population largely aligns with results obtained from the FAS although the favourable trend towards palivizumab increases: 14/443 and 10/437 participants met the pre-specified RSV-associated MALRI. This trend in efficacy is driven by a difference of 4 cases but the overall low number of cases impede precise estimates.

Among RSV-associated MALRI, a comparable proportion of cases had rales/crackles (14.3% MK-1654 vs 16.7% palivizumab), while more infants in the MK-1654 group (57.1%) reported with wheezing in comparison to the palivizumab group (25.0%). As regards the severity indicator, the majority of cases reported tachypnoea in both treatment arms (57.1% MK-1654 vs 75.0% palivizumab), followed by chest-wall indrawing (28.6% MK-1654 vs 58.3% palivizumab), and hypoxemia (28.6% MK-1654 vs 41.7% palivizumab). The observed imbalances in the components used for the MALRI case definition are due to a small numerical difference in case numbers.

The incidence rate of **RSV-associated Hospitalizations** from Days 1 through **150 postdose** 1 in RSV Season 1 was comparable among study arms (0.013 [5 cases among 443 infants] in the MK-1654 group and 0.015 [6 cases among 437 infants] in the palivizumab group), similarly, to the incidence rate of **RSV-associated severe MALRI**, evaluated as exploratory endpoint (0.010 [4 cases among 443 infants] in the MK-1654 group vs 0.015 [6 cases among 437 infants] in the palivizumab group). Regarding the descriptive components of the case definition, severe RSV-associated MALRI cases were comparable between treatment arms.

Anti-drug antibodies

Anti-drug antibodies (ADA) positivity increased over time across both pivotal studies. The incidence rate of RSV-associated MALRI was higher in ADA-positive participants with respect to ADA-negative participants in both pivotal studies. For instance, the incidence rate (95% CI) was 0.125 (0.068, 0.209) in ADA-positive participants (14 cases among 120 participants) and 0.022 (0.016, 0.030) in ADA-negative participants (41 cases among 1898 participants) when considering ADA status at day 150 in Study MK-1654-004. Similarly, the incidence rate (95% CI) was 0.256 (0.053, 0.748) in ADA-positive participants (3 cases among 13 participants) and 0.030 (0.013, 0.059) in ADA-negative participants (8 cases among 273 participants) when considering ADA status at day 150 in Study MK-1654-007. The interpretability of these observations is impeded by the fact that samples for immunogenicity assessments were taken earliest at Day 150 postdose, which also coincides with the earliest time point for efficacy analyses. In addition, the sample size for ADA-positive participants was small with respect to ADA-negative participants. Hence, the impact on ADA development on efficacy is inconclusive. It is reassuring that no trend between ADA positivity and reduced SNA titers was identified and no concern for single dose administration arises (please refer to the Clinical Pharmacology section). However, the ADA incidence increased over time, which may have implications for repeat-dosing. As for the time being the clinical implications on efficacy remain unclear, this will be considered as uncertainty.

Antiviral resistance

Across both studies, 14 clesrovimab-treated participants had substitutions detected in site IV of the RSV F protein. Out of those instances, the G446 residue (G446E, G446R, G446W) was affected in 11 participants out of which 2 presented with RSV-associated MALRI (1 severe though), both enrolled in Study MK-1654-007. It is considered plausible that the underlying condition of the affected participant (CHD) may have been linked to the severity of the lower respiratory tract infection. In addition, one participant with a G446W substitution enrolled in Study MK-1654-004 reported an RSV-associated hospitalisation but did not qualify as MALRI case. It is unknown whether infants were infected with naturally circulating G446 variants or whether these variants emerged due to selective pressure in the presence of clesrovimab (or a mixture of both). As no G446 substitutions were detected in the placebo or palivizumab arm, the latter scenario appears plausible. It is reassuring though that no other variants associated with MARM were detected across Study MK-1654-004 and Study MK-1654-007. Overall, the genetic stability of Site IV seems to be well conserved, also between RSV A and RSV B, and less vulnerable to selective pressure (Nuttens et al., 2024). In addition, no clear picture on unusually clinical courses due to MARM or variants in the site IV of the F protein emerged. From a precautionary

view, the occurrence of the MARM G446E (due to natural circulation or within-host evolution) and other variants of the residue G446 as well as substitutions within site IV is a potential concern although no clear clinical impact can be deduced currently. Along the D120 responses, the Applicant communicated that currently a feasibility assessment entailing a prospective multi-country RSV strain surveillance study is ongoing, which is appreciated.

2.6.7. Conclusions on the clinical efficacy

Presented results demonstrate that a single 105 mg dose of MK-1654 decreases the incidence of RSV-associated MALRI and severe MALRI in infants and neonates during their first RSV season. The effect is considered clinically relevant by the CHMP. Efficacy outcomes are supported by secondary and exploratory endpoints, with a trend towards a higher efficacy with increasing disease severity.

As regards infants at increased for risk for RSV disease, Study MK-1654-007 is supportive in demonstrating efficacy in children with increased risk of severe RSV symptoms due to prematurity (GA <35 weeks), hemodynamically significant CHD or CLD of prematurity. While efficacy is being inferred by extrapolation from healthy infants based on comparable exposure, the provided efficacy data up to date indicate that MK-1654 and palivizumab exert comparable efficacy against RSV-associated MALRI in RSV Season 1, supported by additional exploratory endpoints including RSV-associated severe MALRI, with results being not of confirmatory nature and the overall low number of cases impedes precise estimates.

Thus, the CHMP is of the view that the claimed indication is supported by the evidence, while no or limited data for infants with a body weight below 1.1 kg and a gestational age of <29 weeks, respectively, are available, which is reflected in the SmPC.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The safety of clesrovimab in infants was evaluated in 4 studies:

- **MK-1654-004 (Phase 2b/3)**: Healthy preterm and full-term infants received either a single dose of clesrovimab (105 mg) or placebo (control) at the beginning of the study.
- **MK-1654-007 (Phase 3)**: In RSV Season 1, infants at increased risk for severe RSV disease received blinded doses of either clesrovimab (105 mg) or palivizumab at Dose 1 and either placebo or palivizumab at Dose 2 before unblinding. Upon unblinding at Day 60, participants in the palivizumab group received at least 1 and up to 3 single doses of palivizumab every 28 days. For participants eligible to continue in RSV Season 2, a dose of clesrovimab (210 mg) was administered (open label) up to 4 weeks before the beginning of the participant's second RSV season.
- **MK-1654-002 (Phase 1b/2a)**: Healthy preterm and full-term infants received a single dose of clesrovimab (100 mg) (Panels D and E) or placebo at the beginning of the study.
- **MK-1654-008 (Phase 1)**: Healthy infants (Panel C) received a single dose of clesrovimab (105 mg) at the beginning of the study.

Table 51. Total number of participants in the overall infant safety database

Population	Study Number	Number of Participants		Total
		Clesrovimab	Control[a]	
Healthy infants	MK-1654-002	64[b]	38	102
	MK-1654-004	2412[c]	1202	3614
	MK-1654-008[d]	25	N/A	25
Infants at increased risk for severe RSV disease	MK-1654-007[e]	446[f]	450	896
Overall population in infant safety database		2947	1690	4637

APaT=all participants as treated; CSR=clinical study report; N/A=not applicable; RSV=respiratory syncytial virus.

[a] Control included participants in MK-1654-002 and MK-1654-004 who received placebo, and participants in MK-1654-007 who received palivizumab.

[b] Study MK-1654-002 includes preterm and full-term infant panels (Panels D and E, respectively) who received a dose of 100 mg clesrovimab (Process 1).

[c] Of the 2412 participants who were dosed with clesrovimab (Process 2), 2409 were included in the APaT population for safety analyses. Three participants were excluded due to being randomized and dosed at 2 different sites. Their safety data are provided in a separate listing in the MK-1654-004 CSR.

[d] Study MK-1654-008 includes infants (Panel C) who received a dose of 105 mg clesrovimab (Process 1).

[e] Study MK-1654-007 includes a subset of 117 participants from Season 1 who were dosed with 210 mg clesrovimab (Process 2) in Season 2.

[f] Of the 446 participants who were dosed with clesrovimab (Process 2), 445 were included in the APaT population for safety analyses. One participant was excluded due to receiving a dose of clesrovimab followed by a dose of palivizumab (instead of placebo). This participant's safety data are provided in a separate listing in the MK-1654-007 CSR.

Sources: [Ref. 5.3.3.1: P002MK1654: Table 10-1] [Ref. 5.3.5.1: P004V01MK1654: Table 10-1] [Ref. 5.3.5.1: P007V01MK1654: Table 10-1] [Ref. 5.3.5.2: P008MK1654: Table 10-1]

Safety analyses were performed in the APaT population, defined as all randomized participants who received at least 1 dose of study intervention. Safety data from MK-1654-004 and MK-1654-007 were not integrated due to differences in the comparators and underlying comorbidities of the infant populations evaluated. Likewise, safety data from the early phase studies in healthy infants (MK-1654-002, MK-1654-008) were not integrated with MK-1654-004 due to differences in formulation and safety assessments.

2.6.8.2. Adverse events

Studies in Healthy Infants

Phase 2b/3 Study (MK-1654-004)

Table 52. Analysis of adverse event summary (all participants as treated population) (Day 1 through 365 postdose)

	MK-1654 105 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	2,409		1,202		
with one or more adverse events	1,861	(77.3)	932	(77.5)	-0.3 (-3.1, 2.7)
injection-site	282	(11.7)	144	(12.0)	-0.3 (-2.6, 1.9)
systemic	1,829	(75.9)	920	(76.5)	-0.6 (-3.5, 2.4)
with no adverse event	548	(22.7)	270	(22.5)	0.3 (-2.7, 3.1)
with drug-related[b] adverse events	696	(28.9)	344	(28.6)	0.3 (-2.9, 3.4)
injection-site	282	(11.7)	144	(12.0)	-0.3 (-2.6, 1.9)
systemic	562	(23.3)	270	(22.5)	0.9 (-2.1, 3.7)
with non-serious adverse events	1,801	(74.8)	908	(75.5)	-0.8 (-3.7, 2.2)
with serious adverse events	278	(11.5)	149	(12.4)	-0.9 (-3.2, 1.3)
with serious drug-related[b] adverse events	1	(0.0)	1	(0.1)	-0.0 (-0.4, 0.2)
who died	7	(0.3)	3	(0.2)	0.0 (-0.5, 0.4)

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
[b] Determined by the investigator to be related to the treatment.
Reported adverse events include 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.
MedDRA version 28.1 was used in the reporting of this study.
CI=Confidence interval.

Source: [P004V01MK1654: adam-adsl; adae]

The most frequently reported (>10%) AEs from Days 1 through 365 postdose in either intervention group were irritability, upper respiratory tract infection, and somnolence. Of the 77.3 % of participants with one or more adverse events in the MK-1654 group and 77.5% in the placebo group experienced following adverse events by descending frequency (Incidence ≥ 5%): irritability (24.2% vs 25.2%), upper respiratory tract infection(14.8% vs 15.7%), somnolence (14.4% vs 16.6%), body temperature increased (8.9% vs 9.2%), nasal congestion (8.5% vs 8.2%), cough (8.3% vs 7.7%), rhinorrhoea (7.1% vs 6%), injection site pain (6.5% vs 8%), diarrhoea (5.8% vs 6.5%), nasopharyngitis (5.8% vs 6,5%) and decreased appetite (6.7% vs 7.7%).

Solicited Adverse Events

The proportions of participants with solicited injection-site and systemic AEs from Days 1 through 5 postdose were generally comparable between the MK-1654 group (34.8%) and the placebo group (34.9%). 11.4 % of participants in the MK-1654 group and 11.7% of participants in the placebo group experienced solicited injection site AEs. 30.1 % of participants in the MK-1654 group and 31.2% of participants in the placebo group experienced solicited systemic AEs.

Table 53. Analysis of Participants With Solicited Adverse Events (All Participants as Treated Population) (Days 1 through 5 postdose)

	MK-1654 105 mg		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	2,409		1,202		
with one or more solicited adverse events	839	(34.8)	420	(34.9)	
with no solicited adverse events	1,570	(65.2)	782	(65.1)	
Solicited injection site adverse events	**274**	**(11.4)**	**141**	**(11.7)**	**-0.4 (-2.6, 1.8)**
Injection site erythema	107	(4.4)	43	(3.6)	0.9 (-0.6, 2.2)
Injection site pain	156	(6.5)	96	(8.0)	-1.5 (-3.4, 0.2)
Injection site swelling	77	(3.2)	38	(3.2)	0.0 (-1.3, 1.2)
Solicited systemic adverse events	**726**	**(30.1)**	**375**	**(31.2)**	**-1.1 (-4.3, 2.1)**
Decreased appetite	131	(5.4)	73	(6.1)	-0.6 (-2.3, 0.9)
Irritability	517	(21.5)	264	(22.0)	-0.5 (-3.4, 2.3)
Somnolence	333	(13.8)	192	(16.0)	-2.2 (-4.7, 0.3)

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable adverse event.
MedDRA version 28.1 was used in the reporting of this study.
CI=Confidence interval.

Source: [P004V01MK1654: adam-adsl; adae]

MK-1654-002 (Phase 1/2 Study)

The proportions of participants with one or more AEs, solicited injection-site AEs and solicited systemic AEs were generally comparable across all study intervention groups. Solicited injection-site and systemic AEs were reported for all dose groups; however, the incidences were low in both preterm and full-term infants (solicited injection site AEs: 6.3%, 6.3%, and 5.3%, for preterm infants, full-term infants, and the placebo group, respectively; solicited systemic AEs: 6.3%, 9.4%, and 23.7% for preterm infants, full-term infants, and the placebo group, respectively). The proportion of participants with solicited AEs did not increase with increasing dose of MK-1654 (solicited injection site AEs: 33.3%, 24.2%, 22.5%, 6.3%, 6.3% for 20mg, 50mg, 75mg, 100 mg preterm, and 100 mg full-term infants; solicited systemic AEs: 33.3%, 24.2%, 22.5%, 6.3%, 9.4% for 20mg, 50mg, 75mg, 100 mg preterm, 100 mg full-term infants).

MK-1654-008 (Phase 1 Study)

For the participants who had a single dose of MK-1654, including all adverse events postdose Days 1 to 42 and serious adverse events throughout the duration of study, 36.0%, 76.0%, and 56.0% of participants in Panel A, B, and C respectively reported at least one AE; 5 (20.0%), 7 (28.0%), and 5 (20.0%) participants in Panel A, B, and C, respectively, reported drug-related AEs.The most frequently reported (≥10%) AE in all 3 panels from Day 1 to Day 42 was upper respiratory tract infection (20.0%, 24.0%, and 24.0% in Panel A, B, and C, respectively). The incidence of other AEs was generally low. No more than 5 participants were reported with one or more solicited injection site AEs (injection site erythema, injection site pain and injection site swelling) in each panel from Day 1 through Day 5 post-dose. Panel C: Only injection site erythema was reported for 2 (8.0%) participants.

Study in Infants at Increased Risk for Severe RSV Disease

Phase 3 Study (MK-1654-007 RSV Season 1)

Table 54. Analysis of Adverse Event Summary (All Participants as Treated Population) (Following Any Dose in RSV Season 1) (MK-1654-007)

	MK-1654 105 mg		Palivizumab		Difference in % vs Palivizumab
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	445		450		
with one or more adverse events	335	(75.3)	358	(79.6)	-4.3 (-9.8, 1.2)
injection-site	71	(16.0)	77	(17.1)	-1.2 (-6.0, 3.7)
systemic	325	(73.0)	357	(79.3)	-6.3 (-11.9, -0.7)
with no adverse event	110	(24.7)	92	(20.4)	4.3 (-1.2, 9.8)
with drug-related[b] adverse events	141	(31.7)	163	(36.2)	-4.5 (-10.7, 1.7)
injection-site	71	(16.0)	77	(17.1)	-1.2 (-6.0, 3.7)
systemic	113	(25.4)	130	(28.9)	-3.5 (-9.3, 2.3)
with non-serious adverse events	315	(70.8)	341	(75.8)	-5.0 (-10.8, 0.8)
with serious adverse events	99	(22.2)	112	(24.9)	-2.6 (-8.2, 2.9)
with serious drug-related[b] adverse events	0	(0.0)	2	(0.4)	-0.4 (-1.6, 0.4)
who died	8	(1.8)	4	(0.9)	0.9 (-0.7, 2.7)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.9)
discontinued drug due to a drug-related[b] adverse event	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.9)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.9)
discontinued drug due to a serious drug-related[b] adverse event	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.9)

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.

[b] Determined by the investigator to be related to the treatment.

Reported adverse events include nonserious adverse events that occurred from Day 1 through the day prior to Dose 2, and 14 days after each subsequent dose, and serious adverse events that occurred through the duration of participation in RSV Season 1.

MedDRA version 28.1 was used in the reporting of this study.

CI=Confidence interval; RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adae]

The most frequently reported (>10%) AEs in the MK-1654 group and the palivizumab group following any dose in RSV Season 1 were irritability, somnolence, upper respiratory infection, and decreased appetite.

Solicited Adverse Events

The proportions of participants with solicited injection-site and systemic AEs from Days 1 through 5 following any dose in RSV Season 1 were generally comparable between the MK-1654 group (44.5%) and the palivizumab group (48.0%). The most frequently reported (>10%) solicited AEs in both intervention groups were irritability, somnolence, and decreased appetite.

Table 55. Analysis of Participants With Solicited Adverse Events (All Participants as Treated Population) (Day 1 Through 5 Following Any Dose in RSV Season 1) (MK-1654-007)

	MK-1654 105 mg		Palivizumab		Difference in % vs Palivizumab
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	445		450		
with one or more solicited adverse events	198	(44.5)	216	(48.0)	
with no solicited adverse events	247	(55.5)	234	(52.0)	
Solicited injection site adverse events	**69**	**(15.5)**	**76**	**(16.9)**	**-1.4 (-6.2, 3.5)**
Injection site erythema	31	(7.0)	27	(6.0)	1.0 (-2.3, 4.3)
Injection site pain	35	(7.9)	51	(11.3)	-3.5 (-7.4, 0.4)
Injection site swelling	29	(6.5)	24	(5.3)	1.2 (-2.0, 4.4)
Solicited systemic adverse events	**180**	**(40.4)**	**195**	**(43.3)**	**-2.9 (-9.3, 3.6)**
Decreased appetite	59	(13.3)	59	(13.1)	0.1 (-4.3, 4.6)
Irritability	133	(29.9)	154	(34.2)	-4.3 (-10.4, 1.8)
Somnolence	88	(19.8)	103	(22.9)	-3.1 (-8.5, 2.3)

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable adverse event.
MedDRA version 28.1 was used in the reporting of this study.
CI=Confidence interval; RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adae]

Phase 3 Study (MK-1654-007 RSV Season 2)

As the study is ongoing, Season 2 was not fully enrolled at the time of data cutoff. A brief summary of available data is provided. The majority (60.7%) of the 117 participants in the APaT population had 1 or more AEs in RSV Season 2 after receiving clesrovimab 210 mg. The proportions of participants with AEs after receiving MK-1654 210 mg in RSV Season 2, were generally comparable, regardless of study intervention received in RSV Season 1 (58.3% vs 63.2%). The most frequently reported (>10% of RSV Season 2 participants) AE was irritability.

Table 56. Adverse Event Summary (All Participants as Treated Population) (Post RSV Season 2 dose, days 1 through 180)

	MK-1654 105 mg (Season 1) + MK-1654 210 mg (Season 2)		Palivizumab (Season 1) + MK-1654 210 mg (Season 2)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	60		57		117	
with one or more adverse events	35	(58.3)	36	(63.2)	71	(60.7)
injection-site	1	(1.7)	1	(1.8)	2	(1.7)
non-injection-site	35	(58.3)	36	(63.2)	71	(60.7)
with no adverse event	25	(41.7)	21	(36.8)	46	(39.3)
with drug-related[a] adverse events	4	(6.7)	7	(12.3)	11	(9.4)
injection-site	1	(1.7)	1	(1.8)	2	(1.7)
non-injection-site	3	(5.0)	7	(12.3)	10	(8.5)
with non-serious adverse events	32	(53.3)	33	(57.9)	65	(55.6)
with serious adverse events	10	(16.7)	9	(15.8)	19	(16.2)
with serious drug-related[a] adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the treatment.
Reported adverse events include nonserious adverse events that occurred from Days 1 through 42 postdose, and serious adverse events that occurred from Days 1 through 180 postdose in RSV Season 2.
MedDRA version 27.0 was used in the reporting of this study.
RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adae]

Solicited Adverse Events

The proportions of participants with solicited injection-site and solicited systemic AEs from Days 1 through 5 post RSV Season 2 dose were generally comparable, regardless of study intervention received in RSV Season 1.

Table 57. Participants With Solicited Adverse Events (All Participants as Treated Population) (Post RSV Season 2 Dose, Days 1 Through 5)

	MK-1654 105 mg (Season 1) + MK-1654 210 mg (Season 2)		Palivizumab (Season 1) + MK-1654 210 mg (Season 2)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	60		57		117	
with one or more solicited adverse events	8	(13.3)	9	(15.8)	17	(14.5)
with no solicited adverse events	52	(86.7)	48	(84.2)	100	(85.5)
Solicited injection site adverse events	**1**	**(1.7)**	**1**	**(1.8)**	**2**	**(1.7)**
Injection site erythema	1	(1.7)	1	(1.8)	2	(1.7)
Injection site pain	0	(0.0)	1	(1.8)	1	(0.9)
Solicited systemic adverse events	**7**	**(11.7)**	**9**	**(15.8)**	**16**	**(13.7)**
Decreased appetite	2	(3.3)	2	(3.5)	4	(3.4)
Irritability	3	(5.0)	9	(15.8)	12	(10.3)
Somnolence	4	(6.7)	1	(1.8)	5	(4.3)

Every participant is counted a single time for each applicable adverse event.
MedDRA version 27.0 was used in the reporting of this study.
RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adae]

Adverse drug reactions

Studies in Healthy Infants

Phase 2b/3 Study (MK-1654-004)

The proportions of participants with AEs related to study intervention from Days 1 through 365 postdose, including injection-site and systemic AEs, were generally comparable between the MK-1654 group (28.9%) and the placebo group (28.6%). All injection-site AEs were determined by the investigator to be related to study intervention. The most frequently reported (>5%) AEs related to study intervention as determined by the investigator from Days 1 through 365 postdose in either intervention group were the solicited events of injection-site pain, somnolence, and irritability.

Table 58 Participants with Adverse Events Related to Study Treatment (Incidence >0% in One or More Treatment Groups) (All Participants as Treated Population) (Days 1 Through 365 Postdose)

	MK-1654 105 mg		Placebo	
	n	(%)	n	(%)
Participants in population	2,409		1,202	
with one or more adverse events related to study treatment	696	(28.9)	344	(28.6)
with no adverse events related to study treatment	1,713	(71.1)	858	(71.4)
Eye disorders	**1**	**(0.0)**	**0**	**(0.0)**
Eye irritation	1	(0.0)	0	(0.0)
Gastrointestinal disorders	**33**	**(1.4)**	**17**	**(1.4)**
Diarrhoea	11	(0.5)	11	(0.9)
Flatulence	9	(0.4)	1	(0.1)
Vomiting	7	(0.3)	1	(0.1)
Constipation	2	(0.1)	2	(0.2)
Abdominal pain	1	(0.0)	0	(0.0)
Abnormal faeces	1	(0.0)	0	(0.0)
Dyschezia	1	(0.0)	0	(0.0)
Dyspepsia	1	(0.0)	1	(0.1)
Frequent bowel movements	1	(0.0)	1	(0.1)
Infantile spitting up	1	(0.0)	0	(0.0)
Mucous stools	1	(0.0)	1	(0.1)
Regurgitation	1	(0.0)	2	(0.2)
General disorders and administration site conditions	**294**	**(12.2)**	**153**	**(12.7)**
Injection site pain[a]	156	(6.5)	96	(8.0)
Injection site erythema[a]	107	(4.4)	43	(3.6)
Injection site swelling[a]	77	(3.2)	38	(3.2)
Fatigue	6	(0.2)	4	(0.3)
Pyrexia	6	(0.2)	4	(0.3)
Injection site bruising	4	(0.2)	2	(0.2)
Discomfort	2	(0.1)	0	(0.0)
Crying	1	(0.0)	2	(0.2)
Injection site haematoma	1	(0.0)	0	(0.0)
Injection site haemorrhage	1	(0.0)	1	(0.1)
Injection site induration	1	(0.0)	2	(0.2)
Injection site macule	1	(0.0)	0	(0.0)
Injection site mass	1	(0.0)	0	(0.0)
Injection site reaction	1	(0.0)	0	(0.0)

	MK-1654 105 mg		Placebo	
	n	(%)	n	(%)
Participants in population	2,409		1,202	
with one or more adverse events related to study treatment	696	(28.9)	344	(28.6)
with no adverse events related to study treatment	1,713	(71.1)	858	(71.4)
Eye disorders	**1**	**(0.0)**	**0**	**(0.0)**
Eye irritation	1	(0.0)	0	(0.0)
Gastrointestinal disorders	**33**	**(1.4)**	**17**	**(1.4)**
Diarrhoea	11	(0.5)	11	(0.9)
Flatulence	9	(0.4)	1	(0.1)
Vomiting	7	(0.3)	1	(0.1)
Constipation	2	(0.1)	2	(0.2)
Abdominal pain	1	(0.0)	0	(0.0)
Abnormal faeces	1	(0.0)	0	(0.0)
Dyschezia	1	(0.0)	0	(0.0)
Dyspepsia	1	(0.0)	1	(0.1)
Frequent bowel movements	1	(0.0)	1	(0.1)
Infantile spitting up	1	(0.0)	0	(0.0)
Mucous stools	1	(0.0)	1	(0.1)
Regurgitation	1	(0.0)	2	(0.2)
General disorders and administration site conditions	**294**	**(12.2)**	**153**	**(12.7)**
Injection site pain[a]	156	(6.5)	96	(8.0)
Injection site erythema[a]	107	(4.4)	43	(3.6)
Injection site swelling[a]	77	(3.2)	38	(3.2)
Fatigue	6	(0.2)	4	(0.3)
Pyrexia	6	(0.2)	4	(0.3)
Injection site bruising	4	(0.2)	2	(0.2)
Discomfort	2	(0.1)	0	(0.0)
Crying	1	(0.0)	2	(0.2)
Injection site haematoma	1	(0.0)	0	(0.0)
Injection site haemorrhage	1	(0.0)	1	(0.1)
Injection site induration	1	(0.0)	2	(0.2)
Injection site macule	1	(0.0)	0	(0.0)
Injection site mass	1	(0.0)	0	(0.0)
Injection site reaction	1	(0.0)	0	(0.0)

	MK-1654 105 mg		Placebo	
	n	(%)	n	(%)
General disorders and administration site conditions	**294**	**(12.2)**	**153**	**(12.7)**
Injection site warmth	1	(0.0)	0	(0.0)
Injection site rash	0	(0.0)	1	(0.1)
Infections and infestations	**3**	**(0.1)**	**1**	**(0.1)**
Conjunctivitis	1	(0.0)	0	(0.0)
Rhinitis	1	(0.0)	0	(0.0)
Upper respiratory tract infection	1	(0.0)	1	(0.1)
Investigations	**26**	**(1.1)**	**11**	**(0.9)**
Body temperature increased	25	(1.0)	11	(0.9)
Faecal volume increased	1	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**83**	**(3.4)**	**54**	**(4.5)**
Decreased appetite[a]	83	(3.4)	54	(4.5)
Musculoskeletal and connective tissue disorders	**1**	**(0.0)**	**1**	**(0.1)**
Pain in extremity	1	(0.0)	0	(0.0)
Floppy infant	0	(0.0)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.1)**
B precursor type acute leukaemia	0	(0.0)	1	(0.1)
Nervous system disorders	**251**	**(10.4)**	**129**	**(10.7)**
Somnolence[a]	248	(10.3)	129	(10.7)
Hypersomnia	1	(0.0)	0	(0.0)
Increased need for sleep	1	(0.0)	0	(0.0)
Tremor	1	(0.0)	0	(0.0)
Psychiatric disorders	**374**	**(15.5)**	**174**	**(14.5)**
Irritability[a]	371	(15.4)	172	(14.3)
Restlessness	4	(0.2)	0	(0.0)
Initial insomnia	1	(0.0)	1	(0.1)
Insomnia	1	(0.0)	1	(0.1)
Nervousness	1	(0.0)	0	(0.0)
Vascular disorders	**1**	**(0.0)**	**0**	**(0.0)**
Flushing	1	(0.0)	0	(0.0)

[a] Injection site erythema, injection site pain, injection site swelling, decreased appetite, irritability, and somnolence were solicited from Days 1 through 5 postdose but may have been reported spontaneously after Day 5 and are included in this table.

Every participant is counted a single time for each applicable adverse event. A participant with multiple adverse events within a system organ class is counted a single time for that system organ class.

Relatedness to study treatment was determined by the investigator.

A system organ class or specific adverse event appears in this table only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Reported adverse events include 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.

MedDRA version 28.1 was used in the reporting of this study.

Source: [P004V01MK1654: adam-adsl; adae]

Phase 1/2 Study (MK-1654-002)

AEs related to study intervention were reported for generally comparable proportions of participants across the study intervention groups through Day 14 and included constipation (3.1% in full term group), injection site pain (6.3% and 2.6% in preterm group and placebo group, respectively),

injection site erythema (3.1%, 3.1%, 2.6% in preterm, full-term, and placebo group, respectively), somnolence (3.1% in full-term group), irritability (3.1%, 6.3%, and 15.8% for preterm, full-term, and placebo, respectively), nasal congestion (3.1% in full term-group), rash maculo-papular (5.3% in full-term group) and rash popular (6.3% in full-term group). All related AEs were considered of mild to moderate intensity.

Phase 1 Study (MK-1654-008)

A total of 12 (16.0%) participants in the three panels reported drug-related systemic AEs. Panel C: Of the 5 (20.0%) participants who reported one or more drug-related systemic AEs, 1 (4.0%) had diarrhea, 1 (4%) had URTI, 1 (4.0%) had decreased appetite, 3 (12.0%) had somnolence, 2 (8.0%) had irritability, and 1 (4.0%) had rash maculo-papular. All drug-related systemic AEs Day 1 to Day 42 reported for participants in each panel were mild to moderate in severity.

Study in Infants at Increased Risk for Severe RSV Disease

Phase 3 Study (MK-1654-007 RSV Season 1)

The proportions of participants with AEs related to study intervention, including injection-site and systemic AEs, were generally comparable between the MK-1654 group (31.7%) and the palivizumab group (36.2%) following any dose in RSV Season 1. All injection-site AEs were considered related to study intervention by the investigator. The most frequently reported (>5%) AEs related to study intervention as determined by the investigator in both intervention groups were the solicited AEs of injection-site pain, decreased appetite, somnolence, and irritability. Injection-site erythema and injection-site swelling considered related to study intervention by the investigator were also reported in >5% of participants in the MK-1654 group.

Table 59. Participants With Adverse Events Related to Study Treatment (Incidence >0% in One or More Treatment Groups) (All Participants as Treated Population) (Following Any dose in RSV Season 1)

	MK-1654 105 mg		Palivizumab	
	n	(%)	n	(%)
Participants in population	445		450	
with one or more adverse events related to study treatment	141	(31.7)	163	(36.2)
with no adverse events related to study treatment	304	(68.3)	287	(63.8)
Gastrointestinal disorders	**3**	**(0.7)**	**2**	**(0.4)**
Constipation	2	(0.4)	0	(0.0)
Flatulence	1	(0.2)	0	(0.0)
Infantile spitting up	1	(0.2)	0	(0.0)
Abdominal pain	0	(0.0)	1	(0.2)
Regurgitation	0	(0.0)	1	(0.2)
General disorders and administration site conditions	**71**	**(16.0)**	**78**	**(17.3)**
Injection site pain[a]	35	(7.9)	51	(11.3)
Injection site erythema[a]	31	(7.0)	27	(6.0)
Injection site swelling[a]	30	(6.7)	24	(5.3)
Injection site inflammation	1	(0.2)	0	(0.0)
Injection site irritation	1	(0.2)	0	(0.0)
Pyrexia	1	(0.2)	3	(0.7)
Discomfort	0	(0.0)	1	(0.2)
Fatigue	0	(0.0)	1	(0.2)
Injection site warmth	0	(0.0)	1	(0.2)
Puncture site erythema	0	(0.0)	1	(0.2)
Infections and infestations	**0**	**(0.0)**	**2**	**(0.4)**
Nasopharyngitis	0	(0.0)	1	(0.2)
Oral candidiasis	0	(0.0)	1	(0.2)
Investigations	**3**	**(0.7)**	**9**	**(2.0)**
Body temperature increased	3	(0.7)	9	(2.0)
Metabolism and nutrition disorders	**33**	**(7.4)**	**31**	**(6.9)**
Decreased appetite[a]	33	(7.4)	31	(6.9)
Nervous system disorders	**43**	**(9.7)**	**63**	**(14.0)**
Somnolence[a]	43	(9.7)	63	(14.0)

	MK-1654 105 mg		Palivizumab	
	n	(%)	n	(%)
Psychiatric disorders	**89**	**(20.0)**	**93**	**(20.7)**
Irritability[a]	88	(19.8)	93	(20.7)
Insomnia	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.4)**	**4**	**(0.9)**
Hypoxia	1	(0.2)	0	(0.0)
Nasal congestion	1	(0.2)	2	(0.4)
Apnoea	0	(0.0)	2	(0.4)
Skin and subcutaneous tissue disorders	**1**	**(0.2)**	**2**	**(0.4)**
Drug eruption	1	(0.2)	1	(0.2)
Rash	0	(0.0)	1	(0.2)
Vascular disorders	**0**	**(0.0)**	**1**	**(0.2)**
Haematoma	0	(0.0)	1	(0.2)

[a] Injection site erythema, injection site pain, injection site swelling, decreased appetite, irritability, and somnolence were solicited from Days 1 through 5 after each dose in RSV Season 1, but may have been reported spontaneously after Day 5 and are included in this table.

Every participant is counted a single time for each applicable adverse event. A participant with multiple adverse events within a system organ class is counted a single time for that system organ class.

Relatedness to study treatment was determined by the investigator.

A system organ class or specific adverse event appears in this table only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Reported adverse events include nonserious adverse events that occurred from Day 1 through the day prior to Dose 2, and 14 days after each subsequent dose, and serious adverse events that occurred through the duration of participation in RSV Season 1.

MedDRA version 28.1 was used in the reporting of this study.

RSV=Respiratory syncytial virus.

Season 2

All injection-site AEs were considered related to study intervention. In total eleven (9.4%) participants had AEs from Days 1 through 180 post RSV Season 2 dose that were considered related to study intervention, thereof 4 (6.7%) in the group previously receiving MK-1654 and 7 (12.3%) in the group previously receiving palivizumab. Related AEs included vomiting, injection site erythema, injection site pain, body temperature increased, somnolence, irritability, dry skin, rash and drug eruption. The most frequently reported (>5%) AE considered related to study intervention was irritability.

2.6.8.3. Serious adverse events, deaths, and other significant events

Studies in Healthy Infants

Phase 2b/3 Study (MK-1654-004)

AEs of special interest

Anaphylaxis/Hypersensitivity

One participant in the MK-1654 group experienced an anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose. This event (Grade 2 bronchospasm on Day 3 postdose) was nonserious and not considered related to study intervention by the investigator. No participants in the placebo group experienced anaphylaxis/hypersensitivity AESI.

Rash

The proportion of participants with rash AESI from Days 1 through 42 postdose was low (≤0.5%) in both the MK-1654 group and the placebo group. All of the events were nonserious and had a maximum

toxicity of Grade 1, except for 1 Grade 3 event. In the MK-1654 group, the majority of participants with rash AESI had events that were not considered related to study intervention by the investigator. The most frequently reported rash AESI in the MK-1654 group was urticaria (≤0.3%; no events of urticaria occurred on Day 1 postdose). One participant in the MK-1654 group had a Grade 3 event of urticaria that occurred on Day 9 postdose and was not considered related to study intervention by the investigator.

In addition to the rash AESI analysis from Days 1 through 42 postdose, an expanded analysis of rash AEs based on specific reported rash PTs from Days 1 through 14 postdose was conducted. The proportion of participants with 1 or more specific rash AEs was generally comparable between intervention groups. All events were nonserious and had a maximum toxicity of Grade 1 or 2 in both intervention groups. A low proportion of participants (0.3% in each intervention group) experienced rash AEs that were considered related to study intervention by the investigator.

Table 60. Participants With Adverse Events of Specific Rash Preferred Terms (Incidence >0% in One or More Treatment Groups) (All Participants as Treated Population) (Days 1 Through 14 Postdose) (MK-1554-004)

	MK-1654 105 mg		Placebo	
	n	(%)	n	(%)
Participants in population	2,409		1,202	
with one or more specific rash adverse events	55	(2.3)	23	(1.9)
with no specific rash adverse events	2,354	(97.7)	1,179	(98.1)
Skin and subcutaneous tissue disorders	**55**	**(2.3)**	**23**	**(1.9)**
Rash	41	(1.7)	11	(0.9)
Rash papular	6	(0.2)	2	(0.2)
Drug eruption	3	(0.1)	2	(0.2)
Dermatitis allergic	2	(0.1)	4	(0.3)
Rash erythematous	2	(0.1)	1	(0.1)
Rash maculo-papular	2	(0.1)	1	(0.1)
Rash vesicular	1	(0.0)	0	(0.0)
Exfoliative rash	0	(0.0)	1	(0.1)
Rash macular	0	(0.0)	2	(0.2)
Toxic skin eruption	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable adverse event. A participant with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA version 27.0 was used in the reporting of this study.

SAEs

The proportions of participants with SAEs from Days 1 through 365 postdose were generally comparable between intervention groups (11.5% in the MK-1654 group and 12.4% in the placebo group). SAEs occurred across multiple SOCs, and no pattern was identified. The most frequently reported SOC was Infections and infestations in both intervention groups.

The proportions of participants with SAEs from Days 365 through 515 postdose were generally comparable between intervention groups (3.1% in the MK-1654 group and 4.0% in the placebo group). SAEs occurred across multiple SOCs, and no pattern was identified. The most frequently reported SOC was Infections and infestations in both intervention groups

Deaths

The proportion of participants who died in RSV Season 1 was 0.3% (n=7 of 2409) in the MK-1654 group, and 0.2% (n=3 of 1202) in the placebo group. One of the 7 participants in the MK-1654 group discontinued from the study due to physician decision on Day 85 and died on Day 487 postdose. Eight of the 10 deaths occurred in participants from South Africa (6 in the MK-1654 group and 2 in the placebo group), which has the highest infant mortality rate among the countries that enrolled

participants. No deaths were reported in participants who were excluded from the APaT population. The AE PTs varied across multiple SOCs:

• MK-1654 group (n=7): death (n=3), sudden infant death syndrome (n=1), staphylococcal sepsis (n=1), aspiration (n=1), pneumonitis (n=1)

• Placebo group (n=3): death (n=1); thermal burn (n=1); coagulopathy, mitral valve disease, COVID-19, COVID-19 pneumonia, acute kidney injury, and acute respiratory failure (all occurred in 1 participant)

There was no pattern identified with respect to cause of death or timing of death relative to study intervention. None of the deaths were considered related to study intervention by the investigator.

Phase 1/2 Study (MK-1654-002)

No AEs of special interest were identified for this study. The proportions of participants with SAEs were generally comparable between intervention groups in preterm and full-term infants through Day 545. The proportion of subjects with one or more SAEs were 9.4%, 18.8%, and 15.8%, in the preterm infants, full-term infants, and placebo groups, respectively. No participant discontinued due to an SAE; all SAEs resolved, and none were considered related to study intervention by the investigator. No deaths occurred.

Phase 1 Study (MK-1654-008)

No AESIs, SAEs, or deaths were reported for infants in this study.

Study in Infants at Increased Risk for Severe RSV Disease

Phase 3 Study (MK-1654-007 RSV Season 1)

AESI

Anaphylaxis/Hypersensitivity

No anaphylaxis/hypersensitivity AESI were reported from Days 1 through 42 post Dose 1 in RSV Season 1.

Rash

Three participants in the MK-1654 group and 1 participant in the palivizumab group had rash AESI from Days 1 through 42 post Dose 1 in RSV Season 1; all events were nonserious and had a maximum toxicity of Grade 1. In the MK-1654 group, 2 of the 3 participants with rash AESI experienced urticaria, neither of which occurred on Day 1 postdose nor was considered related to study intervention by the investigator. The third participant experienced drug eruption, which was considered related to study intervention by the investigator.

In addition to the rash AESI analysis from Days 1 through 42 post Dose 1 in RSV Season 1, an expanded analysis of rash AEs based on specific reported rash PTs from Days 1 through 14 post Dose 1 in RSV Season 1 was conducted. Based on this analysis, the proportion of participants with 1 or more specific rash AEs was generally comparable between intervention groups. All events were nonserious and had a maximum toxicity of Grade 1 in both intervention groups. No participant in the MK-1654 group and 1 participant in the palivizumab group had an event that was considered related to study intervention by the investigator.

Table 61. Participants With Adverse Events of Specific Rash Preferred Terms (Incidence >0% in One or More Treatment Groups) (All Participants as Treated Population) (Post Dose Days 1 Through 14) (MK-1654-007

	MK-1654 105 mg		Palivizumab	
	n	(%)	n	(%)
Participants in population	445		450	
with one or more specific rash adverse events	3	(0.7)	8	(1.8)
with no specific rash adverse events	442	(99.3)	442	(98.2)
Skin and subcutaneous tissue disorders	**3**	**(0.7)**	**8**	**(1.8)**
Rash	2	(0.4)	5	(1.1)
Toxic skin eruption	1	(0.2)	0	(0.0)
Rash maculo-papular	0	(0.0)	3	(0.7)

Every participant is counted a single time for each applicable adverse event. A participant with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears in this table only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA version 27.0 was used in the reporting of this study.
RSV=Respiratory syncytial virus.

SAEs

The proportions of participants with SAEs following any dose in RSV Season 1 were generally comparable between intervention groups (22.2% in the MK-1654 group and 24.9% in the palivizumab group). SAEs occurred across multiple SOCs, and no pattern was identified. The most frequently reported SOC was Infections and infestations in both intervention groups.

Deaths

The proportion of participants who died following any dose in RSV Season 1 was 1.8% (n=8 of 445) in the MK-1654 group and 0.9% (n=4 of 450) in the palivizumab group. No deaths were reported in participants who were excluded from the APaT population. Of the 12 deaths, 7 occurred in infants with CHD (5 in the MK-1654 group and 2 in the palivizumab group) and 5 occurred in preterm infants ≥29 weeks gestational age who did not have CHD or CLD (3 in the MK-1654 group and 2 in the palivizumab group). The AE PTs varied across multiple SOCs:

• MK-1654 group (n=8): cardiac dysfunction (n=1); myocardial infarction (n=1); death (n=1); hypoxia (n=1); shunt occlusion (n=1); skull fracture (n=1); interstitial lung disease (n=1); hypoxia and pneumonia (occurred in 1 participant)

• Palivizumab group (n=4): sudden infant death syndrome (n=1); pneumonia (n=1); pulmonary alveolar hemorrhage (n=1); brain injury, pulmonary congestion, and cyanosis (all occurred in 1 participant) There was no pattern identified with respect to cause of death or timing of death relative to study intervention. The deaths were largely attributable to underlying comorbidities or other identifiable causes. None of the deaths were considered related to study intervention by the investigator. At the time this study was conducted, the global infant mortality rate (including both healthy infants and infants with underlying comorbidities) was 27.94 deaths per 1000 live births.

Phase 3 Study (MK-1654-007 RSV Season 2)

No participants experienced anaphylaxis/hypersensitivity AESI from Days 1 through 42 post RSV Season 2 dose.

One participant had a rash AESI from Days 1 through 42 post RSV Season 2 dose (nonserious, Grade 1 drug eruption on Day 2) considered related to study intervention by the investigator; this participant received palivizumab in RSV Season 1. In RSV Season 2, 19 (16.2%) participants had ≥1 SAE up to Day 180 after the RSV Season 2 dose; none were considered related to study intervention by the

investigator. As of the data cutoff for this marketing application, no deaths were reported during RSV Season 2.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product

Studies in Healthy Infants

Phase 2b/3 Study (MK-1654-004)

Intervention-related AESI

Four participants experienced a rash AESI related to study intervention in the MK-1654 group compared to two participants in the placebo group.

• One participant experienced an event of urticaria (Grade 1) and conjunctivitis on Day 5 postdose. The event of urticaria resolved after 2 days (Day 6).

• One participant experienced an event of urticaria (Grade 1) on Day 2 postdose, which resolved after 10 days (Day 11).

• One participant experienced an event of drug eruption (Grade 1) on Day 2 postdose, which resolved after 2 days (Day 3).

• One participant experienced an event of drug eruption (Grade 1) on Day 2 postdose, which resolved after 21 days (Day 22).

Intervention-related SAEs

Two participants each had 1 intervention-related SAE as determined by the investigator from Days 1 through 365 postdose:

• One participant in the MK-1654 group had a Grade 1 intervention-related SAE of body temperature increased (maximum temperature of 38 °C), which occurred on Day 4 postdose, lasted 10.75 hours, and resolved.

• One participant in the placebo group had a Grade 4 intervention-related SAE of B precursor type acute leukemia, which occurred on Day 3 postdose and had not resolved as of the data cutoff date.

Study in Infants at Increased Risk for Severe RSV Disease

Phase 3 Study (MK-1654-007 RSV Season 1)

None of the SAEs in the MK-1654 group were considered related to study intervention by the investigator. Two participants in the palivizumab group each had 1 intervention-related SAE of apnoea.

One participant in each group had an AESI of rash (drug eruption) that was considered related.

Phase 3 Study (MK-1654-007 RSV Season 2)

None of the SAEs were considered related to study intervention by the investigator.

One participant, who had received palivizumab in RSV Season 1, had a rash AESI (Grade 1 drug eruption) considered related to study intervention in the 42 days after the RSV Season 2 dose. The event occurred 2 days post RSV Season 2 dose, was not serious, and resolved in 1.43 weeks. This participant was ADA negative in RSV Season 2.

2.6.8.4. Laboratory findings

No clinical laboratory evaluations were collected for the infant studies MK-1654-002, MK-1654-004, MK-1654-007, and MK-1654-008.

Vital signs (heart rate, respiratory rate, and body temperature) were prespecified to be reported in MK-1654-002 and MK-1654-008. No clinically meaningful differences in mean change from baseline over time were observed.

In studies MK-1654-004 and MK-1654-007, body temperature measurement was the only vital sign prespecified to be reported. As specified in the MK-1654-004, MK-1654-007, and MK-1654-008 protocols, fever was defined as any rectal temperature ≥102.2 °F (≥39.0 °C) or axillary temperature ≥ 101.7 °F (≥38.7 °C). In MK-1654-002, elevated body temperature was defined using the same cutoffs and is considered to be equivalent to fever.

Body Temperature Measurement

Studies in healthy infants

MK-1654-004

A low proportion (≤1.2% in either intervention group) of participants met the protocol-specified definition of fever from Days 1 through 5 postdose in either intervention group. The proportions of participants with AEs of pyrexia or body temperature increased were generally comparable between intervention groups.

Studies in infants at increased risk

MK-1654-007

RSV Season 1

Following any dose in RSV Season 1, the proportions of participants with protocol-defined fever were low (≤1.3% in either intervention group). Most (>97%) participants in both intervention groups had a maximum body temperature <100.4° F (38.0° C) within Days 1 through 5 after their respective doses in RSV Season 1. Of those with a maximum body temperature ≥100.4° F (38.0° C), the majority had a maximum body temperature <102.2° F (39.0° C) in both intervention groups. One participant in each intervention group experienced a maximum body temperature between ≥104.0° F (40.0° C) and <104.9° F (40.5° C) following any dose.

RSV Season 2

One participant who received palivizumab in RSV Season 1 had a protocol-defined fever based on a maximum axillary temperature ≥101.7° F (38.7° C) within Days 1 to 5 post RSV Season 2 dose. The majority (94.0%) of participants had a maximum body temperature <100.4° F (38.0° C) within Days 1 through 5 post RSV Season 2 dose. Of those with a maximum body temperature ≥100.4° F (38.0° C), all were <102.2° F (39.0° C). Four participants reported pyrexia and 10 participants reported body temperature increased in RSV Season 2.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Healthy infants by subgroups (Study MK-1654-004)

In study MK-1654-004 subgroups were analysed based on the demographic variables gestational age, chronological age, body weight, sex, race, ethnicity, and hemisphere region at randomization.

The proportions of participants with intervention-related systemic AEs (specifically irritability and somnolence, which were solicited) were higher in both intervention groups in White, Northern Hemisphere, and Not Hispanic or Latino participants, compared with their counter subgroups in the same category.

The proportions of participants with SAEs were higher in both intervention groups in early and moderate preterm infants compared with late preterm and full-term infants. In the MK-1654 group the proportions of infants who experienced serious adverse events were 20.7% and 9.6% in the late preterm and full-term infants, respectively. In infants receiving placebo, 20.6% and 10.7% of participants in the in the late preterm and full-term groups, respectively, reported SAEs. In infants receiving MK-1654, 15.7% and 9.2% of participants in the <5kg body weight and ≥5kg body weight groups, respectively, reported SAEs. In infants receiving placebo, 15.9% and 10.5% of participants in the <5kg body weight and ≥5kg body weight groups, respectively, reported SAEs.

Safety results (based on AE summary and solicited AE data) were generally comparable across the subgroups based on the demographic variables analyzed and consistent with the overall population.

Infants at risk

In study MK-1654-007, subgroups were analysed based on participant condition, chronological age, body weight, and hemisphere at randomization, sex, race, and ethnicity for RSV season 1.

The proportions of participants with any AEs (specifically systemic AEs and nonserious AEs) were higher in both intervention groups in participants in the Southern Hemisphere, compared with participants in the Northern Hemisphere. The proportions of participants in the MK-1654 group with solicited AEs of irritability were higher in participants who were female compared to male, and generally comparable to the results in those who received palivizumab.

Drug related AEs were reported in infants at risk <6 months in 30.6% and 32.6% of participants receiving MK-1654 and palivizumab, respectively, and in infants at risk ≥6 months of age in 43.2% and 60% of participants receiving MK-1654 and palivizumab, respectively. In infants at risk, 29% and 33.6% of participants <5kg body weight reported drug related adverse events. In the ≥5kg body weight sub-group, 41.2% and 47.6% of participants receiving MK-1654 and palivizumab, respectively, reported drug related adverse events.

ECMO or Cardiopulmonary Bypass

In RSV Season 1, 15 participants underwent ECMO or cardiopulmonary bypass (per protocol, 5 received an additional dose of their allocated drug since the RSV season was considered ongoing by the investigator). One of the 3 participants who received an additional dose of clesrovimab experienced an AE after the additional dose. This AE (Grade 2 upper respiratory tract infection) was nonserious and not considered related to study intervention.

Evaluation of measurement of clesrovimab levels before and after ECMO or cardiopulmonary bypass as well as after re-dosing of clesrovimab did not raise safety concerns.

Within each of the subgroup categories, the proportions of participants with intervention related AEs were overall comparable between intervention groups in RSV Season 1.

Table 62. Adverse Event Summary by Participant Condition (All Participants as Treated Population) (RSV Season 1)

	CLD				CHD				Neither CLD nor CHD <29 Weeks Gestational Age				Neither CLD nor CHD ≥29 Weeks Gestational Age			
	MK-1654 105 mg		Palivizumab		MK-1654 105 mg		Palivizumab		MK-1654 105 mg		Palivizumab		MK-1654 105 mg		Palivizumab	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	123		126		52		49		26		24		244		251	
with one or more adverse events	94	(76.4)	104	(82.5)	43	(82.7)	41	(83.7)	18	(69.2)	20	(83.3)	180	(73.8)	193	(76.9)
injection-site	24	(19.5)	23	(18.3)	8	(15.4)	11	(22.4)	3	(11.5)	3	(12.5)	36	(14.8)	40	(15.9)
systemic	90	(73.2)	103	(81.7)	42	(80.8)	41	(83.7)	18	(69.2)	20	(83.3)	175	(71.7)	193	(76.9)
with no adverse event	29	(23.6)	22	(17.5)	9	(17.3)	8	(16.3)	8	(30.8)	4	(16.7)	64	(26.2)	58	(23.1)
with drug-related[a] adverse events	43	(35.0)	44	(34.9)	19	(36.5)	24	(49.0)	6	(23.1)	8	(33.3)	73	(29.9)	87	(34.7)
injection-site	24	(19.5)	23	(18.3)	8	(15.4)	11	(22.4)	3	(11.5)	3	(12.5)	36	(14.8)	40	(15.9)
systemic	34	(27.6)	32	(25.4)	16	(30.8)	21	(42.9)	4	(15.4)	6	(25.0)	59	(24.2)	71	(28.3)
with non-serious adverse events	85	(69.1)	102	(81.0)	38	(73.1)	37	(75.5)	17	(65.4)	18	(75.0)	175	(71.7)	184	(73.3)
with serious adverse events	31	(25.2)	39	(31.0)	19	(36.5)	20	(40.8)	6	(23.1)	4	(16.7)	43	(17.6)	49	(19.5)
with serious drug-related[a] adverse events	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)

	CLD				CHD				Neither CLD nor CHD <29 Weeks Gestational Age				Neither CLD nor CHD ≥29 Weeks Gestational Age			
	MK-1654 105 mg		Palivizumab		MK-1654 105 mg		Palivizumab		MK-1654 105 mg		Palivizumab		MK-1654 105 mg		Palivizumab	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
who died	0	(0.0)	0	(0.0)	5	(9.6)	2	(4.1)	0	(0.0)	0	(0.0)	3	(1.2)	2	(0.8)

[a] Determined by the investigator to be related to the treatment.
Reported adverse events include nonserious adverse events that occurred from Day 1 through the day prior to Dose 2, and 14 days after each subsequent dose, and serious adverse events that occurred through the duration of participation in RSV Season 1.
MedDRA version 28.1 was used in the reporting of this study.
RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adae]

2.6.8.7. Immunological events

ADA and NAb Assay

The Applicant has presented an electrochemiluminescence immunoassay for the determination of anti-MK-1654 antibodies in human serum. All critical reagents, drugs, matrices and antibodies and used lot numbers were well described. The assay was validated with respect to cut-points (screening, confirmatory, titre), assay precision, selectivity, haemolytic/lipemic serum, drug tolerance, prozone effect, specificity, and stability (short-term, freeze/thaw). It was set up correctly and is considered state of the art. Presented validation results from three different sites are comparable and the assay is considered valid for its intended use. No standalone Nab assay has been developed by the Applicant. However, the presented approach to conclude that ADA does not have neutralizing effect on clesrovimab activity is found acceptable. It could be shown that there is no systematic trend between ADA positivity and reduced SNA titers when evaluating data from clinical studies MK-1654-004 and MK-1654-007.

Immunogenicity and Safety

358 participants in the MK-1654-004 study were ADA positive, and the proportions of participants with SAEs were generally comparable between ADA-positive (11.7%) and ADA-negative participants (11.9%). No anaphylaxis/hypersensitivity AESI or rash AEs were reported in the ADA-positive subgroups at Day 150.

38 participants in the MK-1654-007 study were ADA positive, and the proportions of participants with SAEs were generally comparable between ADA-positive (23.7%) and ADA-negative participants (22.7%). No anaphylaxis/hypersensitivity AESI or rash AEs were reported in the ADA-positive subgroups in Season1.

Overall, no safety concerns related to ADA arise from the presented safety data.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Due to the mode of action of MK-1654, no altered PK/PD relevant to safety is expected from drug-drug interactions.

Concomitant use with routine childhood vaccination

Study MK-1654-004 – study in healthy infants

When clesrovimab was co-administered with routine childhood vaccinations (within ±7 days), the safety results (based on AE summary and predefined systemic AE data) were generally comparable to safety results when clesrovimab and routine childhood vaccines were administered alone.

Table 63. Adverse Event Summary by Subgroup of Receipt or No Receipt of a Routine Childhood Vaccine Within 7 Days Prior to or After Study Treatment (All Participants as Treated Population) (Days 1 Through 42 Postdose)

	Routine Childhood Vaccination Within 7 Days Prior to or After Study Treatment				No Routine Childhood Vaccination Within 7 Days Prior to or After Study Treatment			
	MK-1654 105 mg		Placebo		MK-1654 105 mg		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	645		317		1,764		885	
with one or more adverse events	495	(76.7)	231	(72.9)	1,324	(75.1)	683	(77.2)
injection-site	82	(12.7)	36	(11.4)	200	(11.3)	108	(12.2)
systemic	481	(74.6)	229	(72.2)	1,305	(74.0)	672	(75.9)
with no adverse event	150	(23.3)	86	(27.1)	440	(24.9)	202	(22.8)
with drug-related[a] adverse events	205	(31.8)	91	(28.7)	491	(27.8)	253	(28.6)
injection-site	82	(12.7)	36	(11.4)	200	(11.3)	108	(12.2)
systemic	166	(25.7)	78	(24.6)	396	(22.4)	192	(21.7)
with non-serious adverse events	487	(75.5)	231	(72.9)	1,314	(74.5)	677	(76.5)
with serious adverse events	23	(3.6)	6	(1.9)	51	(2.9)	48	(5.4)
with serious drug-related[a] adverse events	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)
who died	2	(0.3)	0	(0.0)	1	(0.1)	0	(0.0)

[a] Determined by the investigator to be related to the treatment.
MedDRA version 28.1 was used in the reporting of this study.

Source: [P004V01MK1654: adam-adsl; adae] [P004V01MK1654: sdtm-cm; suppcm]

Predefined systemic adverse events included decreased appetite, irritability and somnolence. When clesrovimab was co-administered with routine childhood vaccinations (within ±7 days), the safety results for the AEs decreased appetite (6.8% in the MK-1654 group vs 9.8% in the placebo group), irritability (24.8% in the MK-1654 group vs 24.9% in the placebo group) and somnolence (17.2% in the MK-1654 group vs 17.7% in the placebo group) were generally comparable to safety results for decreased appetite (6.6% in the MK-1654 group vs 7% in the placebo group), irritability (23.9% in the MK-1654 group vs 25.3% in the placebo group) and somnolence (13.4% in the MK-1654 group vs 16.2% in the placebo group) when clesrovimab and routine childhood vaccines were administered alone.

Study MK-1654-007 – study in infants at increased risk for severe RSV disease

Of the 445 participants in the MK-1654 group, 121 received a childhood vaccine within ±7 days of the dose of MK-1654 in RSV Season 1. When clesrovimab was co-administered with routine childhood vaccinations (within ±7 days), the safety results (based on AE summary and predefined systemic AEs) were generally comparable with the safety results when clesrovimab was administered alone.

Table 64. Adverse Event Summary by Subgroup of Receipt or no Receipt of a childhood Vaccine within 7 Days prior to or After Study Treatment (All Participants as Treated Population) (Participants Treated with MK-1654 105 mg in RSV Season1) (Post Dose 1 Days through 42, RSV Season 1)

	Routine Childhood Vaccination Within 7 Days Prior to or After Study Treatment		No Routine Childhood Vaccination Within 7 Days Prior to or After Study Treatment	
	n	(%)	n	(%)
Participants in population	121		324	
with one or more adverse events	86	(71.1)	240	(74.1)
injection-site	22	(18.2)	49	(15.1)
systemic	83	(68.6)	233	(71.9)
with no adverse event	35	(28.9)	84	(25.9)
with drug-related[a] adverse events	44	(36.4)	97	(29.9)
injection-site	22	(18.2)	49	(15.1)
systemic	37	(30.6)	76	(23.5)
with non-serious adverse events	84	(69.4)	231	(71.3)
with serious adverse events	8	(6.6)	38	(11.7)
with serious drug-related[a] adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	2	(0.6)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related[a] adverse event	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the treatment.
MedDRA version 28.1 was used in the reporting of this study.
RSV=Respiratory syncytial virus.

Source: [P007V01MK1654: adam-adsl; adae] [P007V01MK1654: sdtm-cm; suppcm]

2.6.8.9. Discontinuation due to adverse events

Discontinuation from study intervention due to AEs was applicable in MK-1654-007 (as participants received more than 1 dose of study intervention).

No participant discontinued study intervention due to an AE in Season 1.

In phase 1/2 study MK-1654-002 and phase 1 study MK-1654-008 there were no discontinuations or study pauses reported due to adverse events.

2.6.8.10. Post marketing experience

Not applicable

2.6.9. Discussion on clinical safety

Safety data collection

The safety evaluation is based on data from 4 studies, a phase 1 study **MK-1654-008**, a phase 1b/2a study **MK-1654-002** and a Phase 2b/3 study **MK-1654-004**, all in healthy preterm and full-term infants and a phase 3 study **MK-1654-007** in infants at increased risk of severe RSV disease. No integrated analysis of safety data based on differences in the comparators, underlying comorbidities of the infant populations evaluated and differences in safety assessments was conducted, which is acceptable. Overall, the safety data collection was appropriately standardised across the two pivotal studies. Adverse event evaluations were coded using MedDRA version 27.0 and included solicited injection-site AEs, solicited systemic AE, anaphylaxis/hypersensitivity and rash AESI, nonserious AES and SAEs. Upon identification that certain participant-reported eDiary entries assessed as solicited

adverse events (AEs) were not entered into the clinical trial database, updated study reports for MK-1654-004 and MK-1654-007 were provided where MedDRA version 28.1 was used for AE coding. The affected solicited AEs included injection-site pain, injection-site erythema, injection-site swelling, decreased appetite, somnolence, and irritability reported during Days 1 to 5 post-dose. All eDiary entries meeting AE reporting criteria were subsequently entered into the clinical database. Consequently, key tables impacted by these updates were regenerated using the same data cutoff date as the original interim Clinical Study Report.

In study MK-1654-004 13.2% of participants in the MK-1654 group and 15.8% of participants in the placebo group had protocol deviations, however the percentage concerning safety reporting was lower with 1.2% and 1.5% of participants respectively, in which cases a participant had a reportable safety event and/or follow up safety event information, that was not reported per the timelines outlined in the protocol. In study MK-1654-007, **23.3% of participants in the MK-1654** group and **47% of participants in the palivizumab group** had **protocol deviations**. 1.6% and 1.3% thereof concerned the safety reporting, **8.4 % and 10.6%** of reported deviations concerned trial procedures, where **safety data** was **not collected using the eDiary**. No further information was given, whether this could have any influence on the AE frequency depicted in the SmPC, nor if other safety data evaluations (AESI, SAEs) in the respective participants were also restricted. As a comparable percentage of these protocol deviations was observed in both groups, and it is not anticipated that further safety information could be obtained from these participants, there are no concerns raised.

Exposure

Safety data from 2947 participants who received at least one dose of Clesrovimab (100 or 105 mg) was presented. The size and duration of the presented safety database is acceptable for a safety assessment. However, the number of infants at increased risk, 446, is considered low, and safety data from ongoing studies MK-1654-004 and MK-1654-007 were not complete. In study MK-1654-004 about 86% of participants completed the study, with either Day 365 (RSV Season 1) or Day 515 (RSV Season 2) as their last visit, and about 7% of participants are ongoing in the study. In study ML-1654-007, only 624 (69.6%) participants completed the RSV Season 1 Day 240 visit. The final CSR with the additional safety data for the MK-1654-004 were provided and there were no new safety findings. For study MK-1654-007 additional safety data for the reporting period 06-FEB-2024 through 26-SEP-2024 were provided. At the present moment, long-term safety data (i.e. follow-up data for more than 1 year) is available for 3191/3614 participants (88%) and 458/901 subjects (50%), respectively, in the two studies. The intended-for-marketing dose of clesrovimab for neonates and infants in their first RSV season is 105 mg administered as a 0.7 mL 150 mg/ml single intramuscular injection, while for infants undergoing cardiac surgery with cardiopulmonary bypass during the RSV season, an additional 105 mg dose is recommended as soon as the infant is stable after surgery to ensure adequate clesrovimab serum levels. In the pivotal study MK-1654-007, only 3 (0.7%) subjects received an unscheduled dose of clesrovimab after undergoing ECMO or cardiopulmonary bypass during the RSV season,hence only very little safety data on an additional 105 mg dose of clesrovimab within the first RSV season is thus available. Measurements of clesrovimab levels in participants, before and after ECMO or cardiopulmonary bypass as well as after redosing, were compared to expected levels. This has, in combination with other studies on anti-RSV F protein monoclonal antibodies, demonstrated that the post-procedure reduction in drug-concentration, supports a recommendation of re-dosing after ECMO or cardiopulmonary bypass.

AE

Healthy infants

In study **MK-1654-004** the proportion of participants with one or more AE was overall comparable between the MK-1654 group (77.3%) and the placebo group (77.5%). The most frequently reported

AEs in the MK-1654 group included irritability (24.2%), upper respiratory tract infection (14.8%) and somnolence (14.4%). The proportions of participants with **solicited injection-site (erythema, pain and swelling)** and **solicited systemic (decreased appetite, irritability, somnolence) AEs** from Days 1 through 5 postdose were generally comparable between the **MK-1654 group (34.8%)** and the **placebo group (34.9%).** In the MK-1654 group 11.4% of participants experienced solicited injection site AEs (6.5% pain, 4.4% erythema and 3.2% swelling) and 11.7% of participants (8 % pain, 3.6% erythema, 3.2 % swelling) in the placebo group. 30.1% of participants in the MK-1654 group experienced solicited systemic AEs (21.5% irritability, 13.8% somnolence and 5.4 % decreased appetite) and 31.2% (22 % irritability, 16 % somnolence and 6.1 % decreased appetite) in the placebo group. The majority of solicited AEs was of toxicity Grade 1 or 2. The proportions of participants with solicited AEs of Grade 3 were low (≤0.2%) in both intervention groups. No Grade 4 solicited AEs were reported. Most of solicited injection-site AEs of erythema and swelling had a maximum size of ≤1 inch (2.5 cm). 2 participants in the MK-1654 group had 3 solicited injection-site AEs of erythema or swelling with a maximum size >5 inches (12.7 cm).

In study **MK-1654-002**, the proportion of patients with one or more AEs was overall comparable between participants receiving 100 mg MK-1654 (preterm infants (81.3%), full term infants (84.4%) from panels D and E, respectively) and the placebo group (86.8%). Although numerical differences were noted for the most common AEs (irritability, nasal congestion, somnolence, upper respiratory tract infection, and diarrhea) between the study groups, these are not considered concerning, as the number of events was small in all cases (range: 1-9 events in the respective subgroups), and there was no apparent trend observed in the larger phase 3 studies. The proportions of subjects experiencing one or more solicited injection site reactions (erythema, pain, swelling) were comparable between the study groups (6.3%, 6.3%, 5.3% for preterm, full-term, and placebo, respectively).

In study **MK-1654-008**, 56.0% of infants (panel C) reported at least one AE from days 1 to 42 post dose, which was lower compared to studies MK-1654-004 and MK-1654-007. The most frequently reported AEs in infants were upper respiratory tract infection (24.0%), somnolence (12.0%), irritability (8.0%), nasopharyngitis (8.0%), eczema (8.0%), and injection site erythema (8.0%), which is in line with findings from placebo controlled clinical trials. Solicited injection site reactions (erythema) were reported in 2 (8.0%) of participants and at least one solicited systemic AE (irritability, drowsiness, and appetite loss) was reported in 3 (12%) participants. Overall, the safety findings from study MK-1654-008 are largely comparable to results from placebo-controlled trials and do not raise concerns.

Infants at increased risk

In **study MK-1654-007** the proportion of participants with one or more AE was overall comparable between the MK-1654 group (75.3%) and the palivizumab group (79.6%). The most frequently reported AEs in the MK-1654 group included irritability (30.8%), somnolence (20%), upper respiratory tract infection (12.6%) and decreased appetite (13.5%). The proportions of participants with **solicited injection-site and systemic AEs** from Days 1 through 5 postdose were **higher than in healthy infants**, however they were generally comparable between the **MK-1654 group (44.5%)** and the **palivizumab group (48.0%)** and the majority of solicited AEs was of toxicity Grade 1 or 2. In the MK-1654 group 15.5% of participants experienced solicited injection site AEs (7.9% pain, 7% erythema and 6.5% swelling) and 16.9% of participants (11.3% pain, 6% erythema, 5.3 % swelling) in the palivizumab group. 40.4% of participants in the MK-1654 group experienced solicited systemic AEs (29.9% irritability, 19.8% somnolence and 13.3% decreased appetite) and 43.3% (34.2% irritability, 22.9% somnolence and 13.1 % decreased appetite) in the palivizumab group. The proportions of participants with solicited AEs of Grade 3 were low (≤0.9%) in both intervention groups. No Grade 4 solicited AEs were reported. Most of solicited injection-site AEs of erythema and swelling had a maximum size of ≤1 inch (2.5 cm). No participants in the MK-1654 group had swelling of >3 inches (7.6 cm). The Applicant provided an update of unresolved/ongoing AEs for the two treatment

groups for both pivotal studies has been provided by the applicant. The updated AE's do not differ in number, type or pattern when compared to the previously reviewed AE's and do not raise further concerns or questions.

ADR

Healthy infants

In study **MK-1654-004**, the proportions of participants with **AEs related to study intervention** from Days 1 through 365 postdose, including injection-site and systemic AEs, were generally comparable between the **MK-1654 group (28.9%)**, and the **placebo group (28.6%)**, with injection-site pain (6.5%), somnolence (10.3%) and irritability (15.4%) being the most frequent. Injection site erythema, injection-site swelling, injection-site pain, rash and urticaria are adequately reflected in the SmPC.

In phase 1/2 study **MK-1654-002**, reports of **AEs related to study intervention** were lower in the preterm infant group (12.5%) compared to full-term patients (25.0%), and patients in the placebo group (18.4%). In phase 1 study **MK-1654-008**, 5 (20%) participants reported experiencing one or more drug related adverse events, the most frequent being somnolence (12%), irritability (8%), and injection site erythema (8%). Overall, results for related AEs in early phase clinical trials are in line with results from study MK-1654-004 with respect to frequency and type of ADRs.

Infants at increased risk

In study **MK-1654-007**, the proportions of participants with **AEs related to study intervention** from Days 1 through 365 postdose, including injection-site and systemic AEs, were generally comparable between the **MK-1654 group (31.7%)** and the **palivizumab group (36.2%)** with injection-site erythema (7%), injection-site swelling (6.7), injection-site pain (7.9%), decreased appetite (7.4%), somnolence (9%) and irritability (19.8%) being the most frequent in the MK-1654 group.

AESI

Healthy infants

In study MK-1654-004 one participant in the MK-1654 group experienced an anaphylaxis/hypersensitivity AESI (Grade 2 bronchospasm on Day 3 postdose), which was nonserious and not considered related to study intervention.

The concern that this could be an anaphylactic/hypersensitivity reaction related to clesrovimab is very unlikely due to the time of debut of symptoms (day 3) as well as duration of symptoms (>7 days) is not compatible with a type-I allergic reaction. In addition, the infant had been treated with medication used in the treatment of respiratory symptoms (salbutamol, ambroxol hydrochloride) as well as prednisolone and antihistamine prior to the administration of clesrovimab.

The proportion of participants with the rash AESI from Days 1 through 42 postdose was low (≤0.5%) in both the MK-1654 group, and the placebo group. All of the events were nonserious and had a maximum toxicity of Grade 1, except for 1 unrelated Grade 3 event of urticaria in the MK-1654 group. Four participants experienced a related rash event (2 times drug eruption and urticaria).

In phase 1/2 study MK-1654-002 and phase 1 study MK-1654-008, no AESIs were identified.

Infants at increased risk

No anaphylaxis/hypersensitivity AESIs were reported from Days 1 through 42 post Dose 1 in RSV Season 1, nor in Season 2. No cases of anaphylaxis/hypersensitivity AESIs were reported in study MK-1654-007 study. For both studies, it appears in the protocols that AESI assessment is based on MedDRA PT's combined with investigator's assessment of being an AESI.

Three participants in the MK-1654 group and 1 participant in the palivizumab group had rash AESI from Days 1 through 42 post Dose 1 in RSV Season 1; all events were nonserious and had a maximum toxicity of Grade 1. In the MK-1654 group, 2 of the 3 participants with rash AESI experienced urticaria, neither of which occurred on Day 1 postdose, nor was considered related to study intervention by the investigator. The third participant experienced drug eruption, which was considered related to study intervention by the investigator. One participant, who received palivizumab in RSV Season 1, had a rash AESI (Grade 1 drug eruption) that was not serious but considered related to study intervention.

SAEs and death

Healthy infants

In **study MK-1654-004**, the proportion of participants experiencing **SAEs** was comparable between the **MK-1654 group (11.5%**), and the **placebo group (12.4%**). The most frequently reported SOC was infections and infestations, and **1 SAE** in each group was considered **related** (**increased temperature** in the MK-1654 group, and B precursor type acute leukemia in the placebo group). 358 participants in the MK-1654-004 study were ADA positive, and the proportions of participants with SAEs were generally comparable between ADA-positive (11.7%), and ADA-negative participants (11.9%). No anaphylaxis/hypersensitivity AESI or rash AEs were reported in the ADA-positive subgroups at Day 150.

There were **7 deaths** (with varying AE PTs including death (3), sudden infant death syndrome (1), staphylococcal sepsis (1), aspiration (1) and pneumonitis (1)) in the MK-1654 group (**0.3%**) and 3 deaths in the placebo group (**0.2%**), none were considered related.

In study **MK-1654-002**, the proportion of subjects who experienced SAEs in the preterm group was lower compared to full term patients, and patients in the placebo group (9.4, 18.8% and 15.8%, respectively). Of these SAEs, none led to study discontinuation, or was considered related to treatment. No deaths were reported. In study **MK-1654-008**, no SAEs and deaths were reported in the infants group (panel C).

Infants at increased risk

In **study MK-1654-007** the proportion of participants with **SAEs** in infants at increased risk was **higher** than in healthy infants, however the percentage was comparable between the **MK-1654 group (22.2%**) and the **palivizumab group (24.9%**) in Season 1, therefore raising no further concerns. The SOC with the most frequently reported SAEs was infections and infestations in both intervention groups (16.2% and 18.4% for MK-1654 and palivizumab, respectively). None of the SAEs in the MK-1654 group was considered related. In RSV Season 2, 19 (16.2%) participants had ≥1 SAE up to Day 180 after the RSV Season 2 dose. The proportions of participants with SAEs were generally comparable, regardless of study intervention received in RSV Season 1. 38 participants in the MK-1654-007 study were ADA positive, and the proportions of participants with SAEs were generally comparable between ADA-positive (23.7%) and ADA-negative participants (22.7%).

The number of deaths was higher in the **MK-1654 group (1.8%)** with **8 deaths** (including varying AE PTs death (1), cardiac dysfunction (1), myocardial infarction(1), hypoxia (1), shunt occlusion (1), skull fracture(1), interstitial lung disease(1), hypoxia and pneumonia (in one patient)) than in in the **palivizumab group (0.9%)** with 4 deaths, however all of the cases had different causes, underlying co-morbidities, none was considered related and the percentage of deaths was in general comparable to the overall infant mortality rate.

19 (**16.2%**) participants had ≥1 **SAE** up to Day 180 after the RSV Season 2 dose. None were considered related to study intervention. With the updated data cutoff (reporting period 06-FEB-2024 through 26-SEP-2024) 1 death was reported for an infant born at 26 weeks with CLD who died on Day

25 post RSV Season 2 dose. The participant received palivizumab in RSV Season 1 and death was not considered related.

Discontinuation due to adverse events

Discontinuations were not evaluated in MK-1654-004, as participants only received a single dose, which is acceptable. The discontinuation rate was in general low, with 6.6% of participants in each group, mainly due to withdrawal by parent/guardian or lost to follow-up.

In study MK-1654-007 no participant discontinued study intervention due to an AE in Season 1. The percentage of discontinuations was low and comparable between the groups with 7.8% in the MK-1654 group and 6.9% in the palivizumab group, mainly due to withdrawal by parent/guardian or lost to follow-up.

No concerns arise from exploratory studies MK-1654-002 as well as MK-1654-008 as there were no discontinuations or study pauses reported due to adverse events.

Safety in special populations

Healthy infants:

In study MK-1654-004, subgroups were analysed based on the demographic variables gestational age, chronological age, body weight, sex, race, ethnicity, and hemisphere region at randomization.

The proportion of subjects with AEs was largely comparable between the demographic subgroups, with some numerical differences based on gestational age, body weight, ethnicity and hemisphere. Overall, differences between the subgroups are not considered concerning due to comparability within the subgroup between MK-1654 and placebo. Concerning body weight, in study MK-1654-004, the level of SAEs was higher in infants weighing less than 5 kg (clesrovimab/placebo: 15.7%/15.6%) compared to infants weighing more than 5 kg (clesrovimab/placebo: 9.2%/10.5%). This is to be expected and since the rates are comparable in the two treatment groups, no concern is raised. The same picture was seen in study MK-1654-007. The lowest body weight of an infant included in the MK-1654-004 and MK-1654-007 study was 1.6 kg and 1.1 kg, respectively. According to the Clinical Overview, page 22 under Clinical Pharmacology, body weight was a significant covariate on clesrovimab PK, however, no actual exposure-safety analyses have been provided. Considering that the smallest and most premature infants presumably will have a higher exposure of clesrovimab, a respective statement in the SmPC on the use of clesrovimab in infants weighing less than 1.1 kg or in infants with lower GA than the lowest GA included in the two studies is included in SmPC section 4.2.

Solicited adverse events (injection and systemic) were overall more common in the northern hemisphere, with irritability and somnolence being more frequent in this patient subgroup. This is not considered concerning due to similarities within the respective sub-population for MK-1654 and placebo.

Infants at risk

In study MK-1654-007, subgroups were analysed based on participant condition, chronological age, body weight, and hemisphere at randomization, sex, race, and ethnicity for RSV season 1. The limited data in patients undergoing cardiopulmonary bypass surgery (n=15) limits conclusions, but no apparent safety concerns were identified.

Overall, drug related adverse events were less frequently reported in infants at risk <6months, and infants <5kg body weight compared to their respective counterpart subgroup, but no difference was noted within the respective subgroup when compared to palivizumab. No notable increases in AEs,

drug related AEs, and SAEs were observed within any subgroup for subjects receiving MK-1654 over palivizumab.

Solicited AEs were in general comparable between MK-1654 and palivizumab, with some differences reported for participants in specific subgroups. Solicited injection site adverse events were reported more frequently in the MK-1654 group compared to palivizumab for the subgroups black or African (19.4% and 14.1%). Solicited systemic AEs were reported more frequently in the MK-1654 group compared to palivizumab for the subgroups CLD (39% and 37.3%), and Asian (39% and 31.3%). Although the number of participants in each subgroup was small, there are notable differences. Both solicited injection site AEs (erythema and swelling) and solicited systemic AEs (irritability and decreased appetite) are higher in the MK-1654 compared to the palivizumab group in participants with CLD. Injection site AEs erythema and swelling are adequately reflected in the SmPC and the frequencies are unlikely to be changed by these results.

Concerning **GA** infants with neither CLD nor CHD aged <29 weeks were compared to >29 weeks, however the group of infants aged <29 weeks was quite small (n=50) compared to the group of infants >29 weeks (n=495). Based on these limited data, the number of AEs generally appeared comparable regardless of GA. For SAEs specifically, the frequency was similar across treatment groups in the infants aged >29 weeks (clesrovimab/palivizumab: 17.6%/19.5%), while for the smallest subgroup of children with GA<29 weeks and no CLD/CHD, the number of SAEs was higher in the clesrovimab group (23.1%, n=26) vs the palivizumab group (16.7%, n=24), albeit low numbers. The overall SAEs are similar in number and pattern between the clesrovimab group (21.6%, n=21) and the palivizumab group (28.7%, n=31) reported in RSV Season 1 with a GA <29 weeks irrespective of CLD/CHD. The patient born at lowest GA treated with clesrovimab was born at GA 23.6 weeks.

For both studies, considering a median age at randomization of 2.5-3 months, AE's have been looked at by age groups at randomization (<3 months; ≥3 to ≤6 months and >6 months) and were found to be similar in both arms across the age-groups in both study MK-1654-004 and study MK-1654-007.

Immunological events

358 participants in the MK-1654-004 study and 38 participants in the MK-1654-007 were ADA positive. No anaphylaxis/hypersensitivity AESI or rash AEs were reported in the ADA-positive subgroups at Day 150 in healthy infants or in Season1 in infants at increased risk. Overall, no safety concerns related to ADA arise from the presented safety data.

Safety related to drug-drug interactions

Concomitant childhood vaccines

In studies MK-1654-004 and MK-1654-007, the proportions of patients experiencing AEs between participants receiving concomitant childhood vaccinations and MK-1654 alone were in general comparable. Although safety events were presented for both subgroups of patients, the Applicant did not present a comparison regarding the type and number of vaccines given to each subgroup. Nonetheless there were no notable differences between infants who received routine childhood vaccines and those who did not.

Healthy infants

In study MK-1654-004, the proportion of patients experiencing one or more AEs was comparable between subjects receiving concomitant vaccinations and those who did not (76.7% and 75.1%, respectively). Predefined systemic AEs (systemic AEs solicited from days 1 through 5 postdose and reported spontaneously after Day 5) were slightly higher in the group receiving concomitant vaccinations compared to MK-654 alone (31.6% and 28.1%, respectively).

Infants at increased risk

In study MK-1654-007, the proportions of patients who received MK-1654 and experienced one or more AEs was comparable between subjects receiving concomitant vaccinations and those who did not (71.1% and 74.1%, respectively). Drug related AEs were higher in the subgroup of subjects receiving concomitant vaccinations compared to those who did not (36.4% and 29.9%), with none of the related AEs being graded as serious. On SOC level, infections and infestations were more frequent in the patient group receiving no concomitant vaccines compared to subjects receiving concomitant vaccines (19.0% vs. 32.7% for patients receiving concomitant vaccines and no concomitant vaccines, respectively).

Laboratory and other findings

No clinical laboratory evaluations were collected for infants in studies MK-1654-002, MK-1654-004, MK-1654-007, and MK-1654-008.

Healthy infants

In study MK-1654-004, the proportion of patients with fever from days 1 through 5 postdose was low in both the MK-1654 group and the placebo group (0.5% and 1.2%, respectively). In study MK-1654-002, one subject (3.1%) in the preterm infant group had a maximum temperature of ≥ 102.2 ºF (39.0 ºC). In study MK-1654-008, none of the subjects in panel C (infants) was reported having fever.

Infants at increased risk

In study MK-1654-007, RSV season 1, the proportion of patients following any dose with fever was lower in the MK-1654 group, compared to the palivizumab group (0.9% vs. 1.3%; 95% CI: -2.1, 1.1), with no subjects in the MK-1654 group experiencing fever post dose 2. In RSV season 2, no subjects in the MK-1654 group and one subject in the palivizumab group reported having fever.

Product information

The ADRs injection-site erythema, injection-site swelling, injection-site pain, urticaria and rash are listed as undesirable effects in 4.8.

2.6.10. Conclusions on the clinical safety

In general, the CHMP considers that the safety profile of MK-1654 was adequately characterised. No major safety differences in comparison to placebo or palivizumab were observed. The majority of participants reported one or more AE, mostly mild or moderate in intensity. The most frequently reported AEs by PT, beside injection site reactions were irritability, upper respiratory tract infection and somnolence. The safety profile in infants at increased risk was overall comparable to the safety in healthy infants, although a higher number of solicited AEs and SAEs was observed in both the MK-1654 and the control group. Although the number of participants in each subgroup was small, there are some differences in the subgroups with CHD/CLD. Both solicited injection site AEs (erythema and swelling) and solicited systemic AEs (irritability) are slightly higher in the MK-1654 compared to the palivizumab group in participants with CLD/CHD. The nature and frequency of the reported adverse events are considered acceptable and do not give rise to concern. Safety data has been up-dated by the applicant during the review. Data on the smallest children (GA <29 weeks, irrespective of CLD/ CHD) have been provided. In this vulnerable group of infants, the proportion of participants with SAE was similar in number and pattern between intervention groups (clesrovimab: 21.6%; palivizumab: 28.7%).

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 65. SVIII.1: Summary of safety concerns

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

Having considered the data in the safety specification, at this stage, the proposed summary of safety concerns, containing no listed concerns, is agreed upon by the CHMP.

2.7.2. Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

Table 66. Part III.3.1: On-going and planned additional pharmacovigilance activities

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

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

Overall conclusions on the PhV Plan

The CHMP, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The CHMP also considered that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

There are no safety concerns identified for clesrovimab. Routine risk minimisation activities are conducted.

Summary of Risk Minimisation Measures

Table Part V.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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

2.7.4. Conclusion

Revised safety data were submitted on 15 December 2025. The MAH confirmed that the risk management plan version 1.0 remains unaffected and no changes are proposed. This is endorsed.

The PRAC considers that the risk management plan version **1.0** is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Non-Conformity of paediatric studies

N/A

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

None requested

2.10.3. Quick Response (QR) code

Not applicable.

2.10.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Enflonsia (clesrovimab) is included in the additional monitoring list as new active substance.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Clesrovimab is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

The aim of the therapy is to reduce the risk of (severe) RSV infection and hospitalisation of RSV infection.

The primary endpoint in study MK-1654-004 was RSV-associated medically attended lower respiratory tract infection (MALRI). Secondary endpoint was RSV-associated hospitalisation. An exploratory endpoint included RSV-associated severe MALRI. In study MK-1654-007 there were no primary efficacy endpoints.

3.1.2. Available therapies and unmet medical need

Current preventive therapies for RSV encompass the monoclonal antibodies palivizumab (SYNAGIS™; EU approval 1999, US approval 1998) and nirsevimab (Beyfortus™; EU approval 2022, , US approval 2023). Palivizumab is approved for the prevention of serious lower respiratory tract disease due to RSV in infants and children with increased risk of severe RSV disease and is given as monthly injection throughout the RSV season. Nirsevimab is an extended half-life mAb, given as single dose, and indicated for the prevention of RSV lower respiratory tract disease in infants during their first RSV season. In August 2024, nirsevimab was granted an extension of indication in the EU in children up to 24 months of age who remain vulnerable to severe RSV disease during their second RSV. US approval for both populations was in 2023. In addition, the vaccine Abrysvo™ is approved in the EU and US since 2023 for the prevention of lower respiratory tract disease caused by RSV in infants from birth through 6 months of age via maternal immunization.

Options for the treatment of RSV consist of primarily supportive care (e.g. oxygen, hydration). Usage of aerosolised antiviral ribavirin is usually restricted to immunosuppressed persons linked to inconvenient administration, questionable benefit, teratogenicity concerns and high cost.

The implementation of preventive interventions is therefore of importance in the management of RSV. The availability of an additional monoclonal antibody, targeting another antigenic site of the RSV F protein, is considered relevant in case of potential development of antiviral resistance and to increase the overall options of preventive RSV measures.

3.1.3. Main clinical studies

Two ongoing global pivotal studies have been conducted in two different populations to support this MAA:

Study MK-1654-004 is a phase 2b/3 double-blind, randomized, placebo-controlled study that included healthy preterm (gestational age ≥29 weeks to <35 weeks) and full-term infants (gestational age ≥35 weeks) (n = 2421 and 1211 randomized to MK-1654 and placebo, respectively).

Study MK-1654-007 is a phase 3 partially blinded, randomized, palivizumab-controlled study that included infants at increased risk for severe RSV disease due to risk factors of CHD, CLD, or prematurity (born at ≤35 weeks gestational age) (n = 450 and 451 randomized to MK-1654 and palivizumab, respectively).

3.2. Favourable effects

In Study MK-1654-004 conducted **in healthy preterm** (gestational age ≥29 weeks to <35 weeks) and late preterm / **full-term infants** (gestational age ≥35 weeks) entering their first RSV season: The point estimate of the primary efficacy outcome, **RSV-associated MALRI** from Day 1 through **Day 150 postdose** for MK-1654 with respect to placebo was 60.4% (95% CI:44.1%-71.9%) in the primary analysis population, the FAS. The primary study objective has thus been met as the lower bound of the 95% CI was >25%. These estimates are based on 60 out of 2398 participants in the MK-1654 group and in 74 out of 1201 participants in the placebo group that met the pre-specified RSV-associated MALRI case definition. Results are supported by analyses based on the PP population and the secondary endpoint considering Day 180 as postdose follow-up. Observed efficacy against RSV-associated MALRI was supported by RSV Subtype although the point estimate was numerically lower against RSV A with respect to RSV B: 44.4% (5.5%, 67.3%) RSV A vs 66.2% (47.2%, 78.3%) RSV B.

For the secondary endpoint of **RSV-associated hospitalisation** from Day 1 through **Day 150 postdose,** the estimate for efficacy (95% CI) of MK-1654 relative to placebo was 84.2% (66.6%, 92.6%). Thus, the statistical success criterion was met as the lower bound of the 95% CI was >0%. These estimates were based on event rates of 9 cases among 2398 participants in the MK-1654 group and in 28 cases among 1201 participants in the placebo group.

Exploratory efficacy analysis on **severe RSV-associated MALRI** from Day 1 through **Day 150 postdose,** resulted in an efficacy of 91.7% (95% CI: 62.9%, 98.1%).

In Study MK-1654-007 conducted in **infants at increased risk** for severe RSV disease due to prematurity, CHD or CLD and entering their first RSV season:

The incidence rate of **RSV-associated MALRI** from Day 1 through **Day 150 postdose** in RSV Season 1 was comparable between MK-1654 and palivizumab: 0.036 in the MK-1654 group and 0.030 palivizumab group. These estimates are based on 14 cases among 443 in the MK-1654 group and 12 cases among 437 participants in the palivizumab group. Comparable trends in incidence rates were also seen in the relevant subgroup according to the participant condition (CHD, CLD and pre-maturity [<29 weeks gestational age without CHD/CLD, ≥29 weeks gestational age without CHD/CLD]) between

MK-1654 and palivizumab arms. Observed differences in incidence rates can likely be attributed to chance findings due to the small number of cases.

The incidence rate of **RSV-associated Hospitalizations** from Days 1 through **150 postdose** in RSV Season 1 was 0.013 (5 cases among 443 infants) in the MK-1654 group and 0.015 (6 cases among 437 infants) in the palivizumab group.

Efficacy of clesrovimab in infants at increased risk for severe RSV disease is extrapolated from healthy infants via PK bridging. PK estimates for infants at increased risk for severe RSV disease generally showed higher exposures compared to healthy preterm and full-term infants. Of note, the exposure-response relationship is relatively flat, and no safety risks are apparent following the observed higher exposure in high-risk infants.

SNA titers correlate with clesrovimab concentrations and no systematic trend between ADA positivity and reduced SNA titer was identified.

3.3. Uncertainties and limitations about favourable effects

The minimum body weight at randomization in Study MK-1654-004 (healthy infants) was 1.6 kg and 1.1 kg in Study MK-1654-007 (at risk infants). While it is acknowledged that not the entire weight range of the target population can be represented in clinical trials, a respective statement for infants < 1.1 kg is included in the SmPC. Furthermore, Study MK-1654-007 included only a few children with a GA <29 weeks (non CLD, non CHD; n = 26) treated with MK-1654, while in total 98 participants with a GA <29 weeks (independent of CLD/CHD) were included among MK-1654-treated participants, with a minimum GA of 23.6 weeks.

The interpretation of demonstrated favourable effects on RSV-associated hospitalisation is limited due to the local differences in admission thresholds. Efficacy against the prevention of severe RSV-associated MALRI were evaluated as an exploratory endpoint without type-I error control.

The lower number of cases due to RSV A decreases the precision of the estimate and the study was overall not powered to determine efficacy per RSV subtype.

Efficacy analyses in principle support a duration of protection for 6 months. However, their interpretation is limited by a low event incidence after 5 months postdose. In addition, no clesrovimab exposure or SNA titer threshold is known to confer protection against RSV.

In Study MK-1654-004, there appears to be a trend for lower efficacy against RSV-associated MALRI in infants ≥6 months of age with respect to infants <6 months of age: 19.5% (95% CI -101.3, 66.8%) vs 65.3% (95% CI 49.5, 76.4%), respectively. This is indicative of a lower benefit in infants above 6 months of age when administered the proposed single dose of 105 mg MK-1654. In addition, in the subgroup of infants >6 months considerably lower exposure was observed. The lower number of cases in the oldest age subgroup with respect to infants <6 months of age is noted though, which impedes the interpretability of the data and the precision of efficacy estimates, as reflected by wide 95% CI.

Anti-drug antibodies (ADA) positivity increased over time across both pivotal studies. The incidence rate of RSV-associated MALRI was higher in ADA-positive participants with respect to ADA-negative participants in both pivotal studies. For instance, the incidence rate (95% CI) was 0.125 (0.068, 0.209) in ADA-positive participants (14 cases among 120 participants) and 0.022 (0.016, 0.030) in ADA-negative participants (41 cases among 1898 participants) when considering ADA status at day 150 in Study MK-1654-004.

Efficacy results from Study MK-1654-007 are not of confirmatory nature.

3.4. Unfavourable effects

The safety profile of MK-1654 was characterised based on the two pivotal studies MK-1654-004 in 2412 healthy infants and MK-1654-007 in 446 infants at increased risk. Supportive data are obtained from healthy infants in phase 1/2 studies MK-1654-002 and MK-1654-008. The majority of participants in both studies experienced one or more AE and was overall comparable between the groups, either placebo in MK-1654-004 (77.3% and 77.5%) or palivizumab in MK-1654-007 (75.3% and 79.6%).

The most common AEs by PT in healthy infants were irritability (24.2%), upper respiratory tract infection (14.8%), and somnolence (14.4%). Solicited injection-site (erythema, pain and swelling) and solicited systemic (decreased appetite, irritability, somnolence) AEs were generally comparable between the MK-1654 group (34.8%) and the placebo group (34.9%) and were mild or moderate in intensity. In the MK-1654 group 11.4% of participants experienced solicited injection site AEs (6.5% pain, 4.4% erythema and 3.2% swelling) and 11.7% (8 % pain, 3.6% erythema, 3.2 % swelling) in the placebo group. 30.1% of participants in the MK-1654 group experienced solicited systemic AEs (21.5% irritability, 13.8% somnolence and 5.4 % decreased appetite) and 31.2% (22 % irritability, 16.2 % somnolence and 6.1 % decreased appetite) in the placebo group.

AEs related to study intervention were reported with a similar frequency between the MK-1654 group (28.9%) and the placebo group (28.6%) with injection-site pain (6.5%), somnolence (10.3%) and irritability (15.4%) being the most frequent in the MK-1654 group.

Overall, the proportion participants with SAEs was comparable between the MK-1654 group (11.5%) and the placebo group (12.4%). The most frequently reported SOC was Infections and infestations, and 1 SAEs in each group was considered related (increased temperature in the MK-1654 group and B precursor type acute leukemia in the placebo group). One participant in the MK-1654 group experienced an anaphylaxis/hypersensitivity AESI (Grade 2 bronchospasm on Day 3 postdose), which was nonserious and not considered related to study intervention. The proportion of participants with rash AESI from Days 1 through 42 postdose was low (≤0.5%) in both groups, with the majority being urticaria with a maximum toxicity Grade 1. One participant in the MK-1654 group had a Grade 3 event of urticaria at day 9 postdose, which was not considered related. Four participants in the MK-1654 group experienced a rash AESI considered related, 2 times urticaria and 2 times drug eruption, all Grade1 and all resolved after a maximum of 21 days.

There were 7 deaths (with varying AE PTs including 1 death, 3 sudden infant death syndrome, 1 staphylococcal sepsis, 1 aspiration and 1 pneumonitis) in the MK-1654 group (0.3%) and 3 deaths in the placebo group (0.2%). Narratives for all cases were provided and none was considered related.

Safety data from the 2 early studies are in line with results obtained for healthy infants in MK-1654-004, with no additional safety findings.

The most common AEs by PT in infants at increased risk were irritability (30.8%), somnolence (20%), upper respiratory tract infection (12.6%) and decreased appetite (13.5%). Solicited injection-site (erythema, pain and swelling) and solicited systemic (decreased appetite, irritability, somnolence) AEs were slightly higher than in healthy infants, however generally comparable between the MK-1654 group (44.5%) and the palivizumab group (48%) with most being mild or moderate in intensity. In the MK-1654 group 15.5% of participants experienced solicited injection site AEs (7.9% pain, 7% erythema and 6.7% swelling) and 16.9% (11.3% pain, 6% erythema, 5.3 % swelling) in the palivizuab group. 40.4 % of participants in the MK-1654 group experienced solicited systemic AEs (29.9% irritability, 19.8% somnolence and 13.3 decreased appetite) and 43.3% (34.2% irritability, 22.9% somnolence and 13.1% decreased appetite) in the palivizumab group.

AEs related to study intervention were reported with a similar frequency between the MK-1654 group (31.7%) and the palivizumab group (36.2%) with irritability (19.8%), somnolence (9%) and injection-site pain (7.9%), being the most frequent in the MK-1654 group.

Overall, the proportion of participants with SAEs was higher in infants at increased risk compared to healthy infants, however frequencies were comparable between the MK-1654 group (22.2%) and the palivizumab group (24.9%). The most frequently reported SOC was infections and infestations in both intervention groups. None of the SAEs in the MK-1654 group was considered related and 2 participants in the palivizumab group had one SAE related to study intervention (apnea).

No anaphylaxis/hypersensitivity AESI were reported from Days 1 through 42 post Dose 1 in RSV Season 1. Three participants in the MK-1654 group and 1 participant in the palivizumab group had rash AESI from Days 1 through 42 post Dose 1 in RSV Season 1, all were nonserious and had a maximum toxicity of Grade 1. 2 of the 3 participants in the MK-1654 group with rash AESI experienced urticaria, one participant experienced drug eruption, which was considered related.

The number of deaths was higher in the MK-1654 group (1.8%) with 8 deaths (including varying AE PTs death, cardiac dysfunction, myocardial infarction, hypoxia, shunt occlusion, skull fracture, interstitial lung disease, hypoxia and pneumonia) than in in the palivizumab group (0.9%) with 4 deaths. Narratives for all of the cases were provided and all had different causes of death, underlying co-morbidities, none was considered related and the percentage of deaths was in general comparable to the overall infant mortality rate.

3.5. Uncertainties and limitations about unfavourable effects

Body weight: Despite the sufficient sample size, safety of clesrovimab in patients weighing less than 1.1 kg is based on extrapolation from heavier infants, as 1.1 kg was the lowest weight of an included patient in the pivotal studies. Similarly, safety in preterm infants with a GA less than the lowest GA included in studies is also extrapolated. Information on the lowest weight and the lowest GA of infants that received clesrovimab was reflected in the SmPC.

3.6. Effects Table

Table 67. Effects Table for Enflonsia for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season (data cut-off: 04-MAR-2024).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
			MK-1654	Placebo		
Number of RSV MALRI	RSV MALRI (≥1 indicator of LRI/severity) through day 150 postdose	n/N	60/2398	74/1201	**Unc**: varying degree in disease severity; uncertainty for a lower effect in infants ≥6 months of age **SoE**: RRR [95% CI] 60.4% [44.1, 71.9]; superiority met (defined as the lower 95% CI of the RRR in RSV MALRI being >25%); supported by day 180 data.	MK-1654-004 CSR
Number of RSV Hospitalisation	Hospital admission for respiratory illness and RSV-positive RT-PCR NP sample	n/N	9/2398	28/1201	**Unc:** Hospital admission thresholds vary between regions **SoE:** RRR [95% CI] 84.2% [66.6, 92.6]; statistical success criterion met (lower bound of 95% CI >0%)	MK-1654-004 CSR
Number of severe RSV MALRI	Severe RSV MALRI through day 150 postdose	n/N	2/2398	12/1201	**Unc**: exploratory EP not type I error controlled **SoE**: RRR [95% CI] 91.7% [62.9, 98.1]; outcome on disease severity	MK-1654-004 CSR
			MK-1654	Palivizumab		
Number and incidence rate of RSV MALRI	RSV MALRI (≥1 indicator of LRI/severity) through day 150	n/N IR [95% CI]	14/443 0.036 (0.020, 0.060)	12/437 0.030 (0.016, 0.053)	**Unc:** no confirmatory evidence, efficacy primarily based on extrapolation from MK-1654-004 **SoE:** comparable trends seen across infant condition subgroup (CHD, CLD, prematurity)	MK-1654-007 CSR
Unfavourable Effects						
			MK-1654 MK-1654	Placebo palivizumab		MK-1654-004
Solicited injection-site AEs		%	11.4 15.5	11.7 16.9		
Solicited systemic AEs			30.1 40.4	31.2 43.3		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Expanded analysis of rash AEs			2.3 0.7	1.9 1.8		Expanded analysis (days 1 through 14 postdose)
SAEs			11.5 22.2	12.4 24.9		

Abbreviations: MALRI = medically attended (outpatient and inpatient) lower respiratory infection; IR = incidence rate; CHD = congenital heart disease; CLD = chronic lung disease; n = number of events; N = number of participants eligible for inclusion in the full analysis set population; RRR = relative risk reduction

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The presented clinical data demonstrate that a 105 mg single dose of MK-1654 decreases the incidence of RSV-associated MALRI in healthy preterm (gestational age ≥29 weeks) and full-term infants during their first RSV season. The prevention of RSV LRI disease is considered an important effect. Thereby, a relative risk reduction of 60.4% (95% CI: 44.1%, 71.9%; p<0.001) in the FAS population is deemed clinically relevant. Notwithstanding, consistent results were achieved in outcomes indicative of severe RSV MALRI and the data generally point towards an increased beneficial effect with increasing disease severity, which is considered clinically most important. Although endpoints on more severe RSV disease outcomes suffer from trade-offs or were of exploratory nature, the totality of evidence is deemed supportive. The evidence of efficacy is overall considered statistically convincing and results obtained from additional sensitivity analyses were consistent with the estimates from the primary analysis.

As regards RSV MALRI efficacy against RSV A vs RSV B, a trend for a lower efficacy against RSV A is noted. However, the RSV subtype distribution cannot be predicted or influenced and the data indicate at least a numerical benefit for MK-1654 vs placebo in preventing MALRI due to RSV A and RSV B, respectively.

Considering that the proposed dosing regimen is a single dose over the entire weight range, efficacy subgroup analyses in relation to body weight are considered important to ensure that consistent favourable effects can be expected and to evaluate whether dose adaptation may be required. The efficacy in preventing RSV associated MALRI was numerically lower in infants ≥6 months of age at dosing but 95% CI widely overlapped. The overall smaller number of enrolled infants of this age subgroup impedes the interpretability of the data and the precision of efficacy estimates, as reflected by wide 95% CI. In addition, estimates obtained across additional efficacy endpoints were consistent with trends from the overall population. It is further understood that infants <6 months of age are especially vulnerable to severe RSV disease outcomes.

The time point of the primary efficacy analysis was 150 days post-dose, with a secondary analysis based on 180 days post-dose follow-up. The surveillance period is deemed clinically relevant to cover a typical RSV season although the timing of dosing for infants born prior the season may differ slightly depending on national recommendations. The Applicant claims a 6-month duration of protection, which is in principle supported by clinical data, but the claim rests solely on efficacy data on the primary

endpoint of Study MK-1654-004 and is limited by a low event incidence that occurred after 5 months postdose. In addition, seemingly roughly half of participants enrolled in temperate regions were dosed after the RSV season peak. In addition, no SNA titer threshold to confer efficacy is known for clesrovimab. These limitations are however reflected in the SmPC.

Results from infants with increased risk to severe RSV disease, including infants GA <29 weeks and infants with CLD of prematurity or hemodynamically significant CHD, were overall similar to palivizumab suggesting comparable favourable effects, and which were consistent among efficacy endpoints and subgroup analysis based on the underlying risk factor. Even though efficacy results were not of confirmatory nature, efficacy of MK-1654 in infants at increased risk for severe RSV disease can be extrapolated via PK bridging, as exposure was higher in this subgroup, predictive of sufficient efficacy. Since the exposure-response relationship is relatively flat, and no safety risks are apparent following the observed higher exposure in high-risk infants, an adjustment of the dose is not considered necessary.

As regards observations of ADA positivity and impact on efficacy, it is reassuring that no trend between ADA positivity and reduced SNA titers was identified. However, the ADA incidence increased over time, which may have implications for repeat-dosing. Hence, the impact on ADA development on efficacy remains inconclusive.

The safety profile of MK-1654 was overall sufficiently characterised. In the two main studies as well as in the supportive phase 1/2 studies submitted in the dossier, no new safety signals were observed for MK-1654 compared to placebo or palivizumab. In infants at increased risk overall more AEs (including solicited AEs as well as SAEs) were observed than in healthy infants, however the frequencies of AEs were balanced between the MK-1654 and the palivizumab group. In both studies the majority of participants experienced 1 or more AEs and the most commonly reported AEs were solicited AEs with mild or moderate intensity.

3.7.2. Balance of benefits and risks

The available clinical data demonstrate that a single-dose of MK-1654 has a clinically relevant beneficial effect with an estimated relative risk reduction of around 60% and 90% in preventing RSV-associated lower respiratory tract disease and severe outcomes, respectively, in neonates and infants during their first RSV season. Uncertainties on the use of clesrovimab in low weight infants is reflected in the SmPC. The safety profile of MK-1654 is in general acceptable with mostly solicited injection-site and systemic AEs of mild to moderate intensity. It is comparable to the safety profile of palivizumab and considered acceptable.

Taking all favourable and unfavourable effects into account, the CHMP is of the opinion that the benefit-risk balance is positive from a clinical point of view.

3.7.3. Additional considerations on the benefit-risk balance

The CHMP received, during the assessment of this application, correspondence from a third party, requesting the CHMP to take into consideration information on use in paediatric patients which is already available in the public domain.

The CHMP considered this intervention in the context of its assessment, noted that the information highlighted by the third-party was already known by the CHMP, and concluded that it had no impact on the CHMP assessment or its conclusions.

3.8. Conclusions

The overall benefit/risk balance of Enflonsia is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Enflonsia is favourable in the following indication(s):

> *"Enflonsia is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.*
>
> *Enflonsia should be used in accordance with official recommendations."*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that clesrovimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0523/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.