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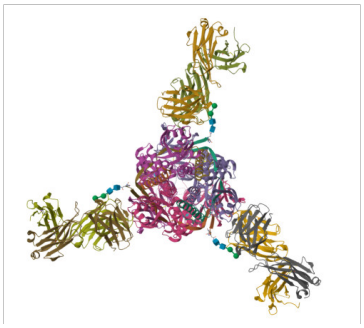


Clesrovimab

Developer(s)

Merck

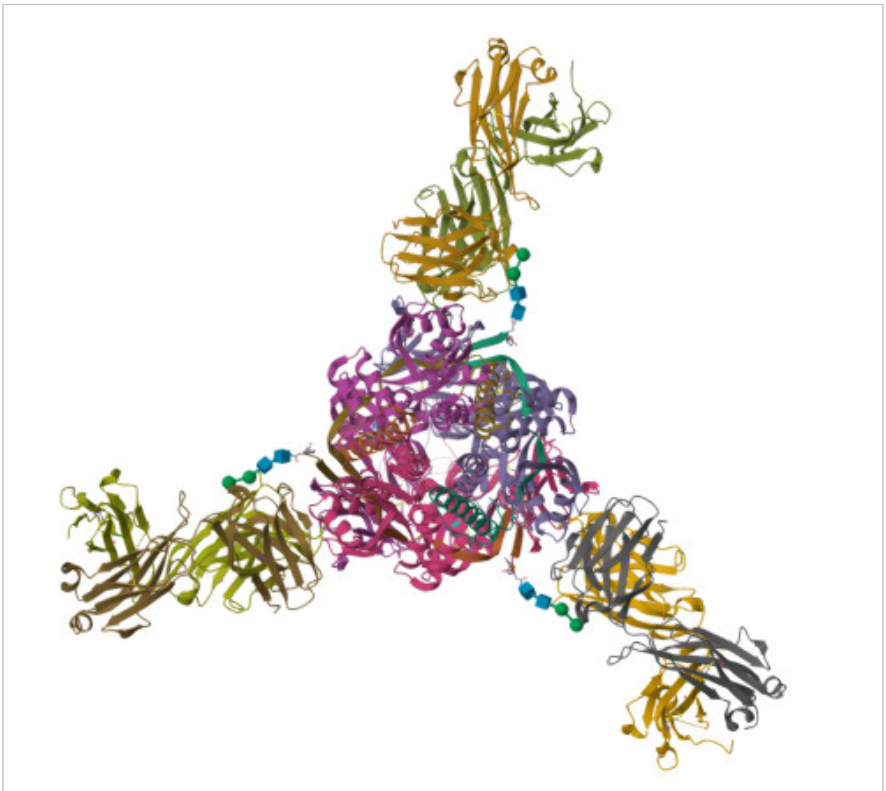
Originator

https://www.merck.com/

United States

Merck & Co., Inc. is an American multinational pharmaceutical company known as Merck Sharp & Drone (MSD) in territories outside of the USA and Canada. Merck was originally established in 1891, and is headquartered in Rahway, New Jersey. The company is particularly well known for developing and manufacturing biologic therapies, vaccines, medicines and animal health products.

Drug structure



Interaction of the parental antibody to MK-1654 (RB1) with the RSV pre-F trimer.

https://doi.org/10.2210/pdb6OUS/pdb

Drug information

Associated long-acting platforms

Monoclonal antibodies and antibody drug conjugates

Administration route

Intramuscular

Therapeutic area(s)

Respiratory syncytial virus (RSV)

Use case(s)

Prevention

Use of drug

Ease of administration

Administered by a nurse
Administered by a specialty health worker
Administered by a community health worker

User acceptance

Not provided

Dosage

Available dose and strength

100 mg in 0.5 mL

Frequency of administration

Not provided

Maximum dose

Not provided

Recommended dosing regimen

Not provided

Additional comments

Not provided

Dosage link(s)

Not provided

Drug information

Drug's link(s)

https://go.drugbank.com/drugs/DB18877

Generic name

Clesrovimab

Brand name

Not provided

Compound type

Biotherapeutic

Summary

Clesrovimab (MK-1654) is an investigational human IgG1 monoclonal antibody (mAb) currently in clinical development for the prevention of Respiratory syncytial virus (RSV). It is being studied as protection against mild, moderate, and severe RSV in preterm, full-term, and at-risk infants during their first RSV season. Clesrovimab is designed to be administered at the same single-dose irrespective of birth weight and exhibits potent in vitro neutralization of RSV-A and RSV-B clinical isolates via high affinity binding to the RSV fusion (F) protein antigenic site IV. Engineered YTE substitution mutations in the mAb fragment crystallizable (Fc) domain result in an extended half-life through enhanced neonatal Fc receptor binding, with a reported half-life in adults ranging from 73 to 88 days.

Approval status

The U.S. Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for clesrovimab (MK-1654), Merck's investigational prophylactic long-acting monoclonal antibody designed to protect infants from respiratory syncytial virus

(RSV) disease during their first RSV season. The FDA has set a Prescription Drug User Fee Act (PDUFA), or target action, date of June 10, 2025.

Regulatory authorities

Unknown

Delivery device(s)

No delivery device

Scale-up and manufacturing prospects

Scale-up prospects

General manufacturing requirements and production scale-up for therapeutic monoclonal antibody (mAb) products is primarily focused on pharmacokinetic suitability, formulation stability and the overall maintenance of product quality. Industrial bioprocessing steps can also potentially introduce additional challenges regarding mAb formulation viscosity and aggregation propensity.

Tentative equipment list for manufacturing

Industrial bioreactor vessel with a production volume capacity of between 5-25kL. Continuous disc stack centrifuges for bioreactor harvesting with subsequent membrane and depth filtration for supernatant clarification. Recombinant protein-A chromatography or other suitable affinity capture apparatus followed by two chromatographic polishing steps such as cation- and anion-exchange. Ultrafiltration membrane system to concentrate and formulate the final product.

Manufacturing

MAbs are highly dependent on their structural, chemical and conformational stability for biological activity. Chemical degradation of mAbs during manufacture can lead to the generation of product variants and complex impurity profiles resulting from a wide range of processes, including: N-linked glycosylation, isomerisation, fragmentation, deamidation, oxidation and C-terminal lysine clipping. Additionally prior to packaging, the final product requires close monitoring for the presence of residual contaminants such as endotoxins and pro-inflammatory peptidoglycans.

Specific analytical instrument required for characterization of formulation

Formulation characterisation steps for therapeutic mAb products include (but are not limited to): (1) Identification of post-translational modifications using ion-exchange chromatography and capillary isoelectric focusing, (2) Measurement of concentration dependent aggregation rates via thermal differential scanning calorimetry, sub-visible particle quantitation and size-exclusion chromatography, and (3) Antibody clipping and fragmentation detection by capillary electrophoresis.

Clinical trials

CLEVER (MK-1654-004)

Identifier

NCT04767373

Link

https://clinicaltrials.gov/study/NCT04767373

Phase

Phase II/III

Status

Completed

Sponsor

Merck Sharp & Dohme LLC

More details

The primary objectives of this phase 2b/3 double-blind, randomized, placebo-controlled study are to evaluate the efficacy and safety of clesrovimab in healthy pre-term and full-term infants. It is hypothesized that clesrovimab will reduce the incidence of respiratory syncytial virus (RSV)-associated medically attended lower respiratory infection (MALRI) from Days 1 through 150 postdose compared to placebo.

Purpose

Efficacy and Safety of Clesrovimab (MK-1654) in Infants (MK-1654-004)

Interventions

Intervention 1

Biological: Clesrovimab

Dosage: Participants receive a single intramuscular (IM) administration of clesrovimab on Day 1.

Intervention 2

Drug: Placebo

Dosage: Placebo (0.9% sodium chloride [NaCL]) solution

Countries

Argentina
Belgium
Canada
Chile
China
Colombia
Denmark
Finland
France
Israel
Italy
Japan
Korea, Republic of
Malaysia
Mexico
Peru
Philippines
Poland
Romania
South Africa
Thailand

Türkiye

United Kingdom

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-04-07

Anticipated Date of Last Follow-up

2025-01-31

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2024-07-09

Actual Completion Date

2024-07-09

Studied populations

Age Cohort

- Children

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Key Inclusion Criteria: * Is a healthy male or female who is an early or moderate pre-term infant (≥29 to 34 weeks and 6 days gestational age) or a late pre-term or full-term infant (≥35 weeks gestational age). * For the phase 2b cohort only: Has a chronological age \>2 weeks of age up to 1 year and is entering their first RSV season at the time of obtaining documented informed consent. * For the phase 3 cohort only: Has a chronological age from birth up to 1 year and is entering their first RSV season at the time of obtaining documented informed consent. * For participants in South Korea only: Weighs ≥2 kg

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

3632

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Double-blind masking

Masking description

Double (Participant, Investigator)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intramuscular

Use case

Prevention

Key results

Not provided

MK-1654-002

Identifier

NCT03524118

Link

https://clinicaltrials.gov/study/NCT03524118

Phase

Phase I/II

Status

Completed

Sponsor

Merck Sharp & Dohme LLC

More details

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics, and incidence of anti-drug antibodies (ADAs) of single ascending doses of clesrovimab in healthy pre-term (born at 29 to 35 weeks gestational age) and full-term (born at >35 weeks gestational age) infants. Participants will be randomized into 1 of 4 dose escalation panels (Panels A to D); an additional panel (Panel E) of full-term infants will receive the same dose as Panel D. Key safety and tolerability variables will be reviewed after each dose panel prior to administering the next-highest dose.

Purpose

Safety, Tolerability, and Pharmacokinetics of Clesrovimab (MK-1654) in Infants (MK-1654-002)

Interventions

Intervention 1

Drug: Clesrovimab

Dosage: Single ascending doses of clesrovimab will be administered via IM injection.

Intervention 2

Drug: Placebo

Dosage: Placebo (0.9% sodium chloride [NaCl]) will be administered via IM injection.

Countries

Chile

Colombia

Korea, Republic of

South Africa

Spain

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2018-09-20

Anticipated Date of Last Follow-up

2025-01-06

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2022-09-14

Actual Completion Date

2022-09-14

Studied populations

Age Cohort

- Children

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Inclusion Criteria: * Is healthy, based on screening safety laboratory, medical history, and physical examination results. * Is a pre-term infant (born at 29 weeks to 35 weeks gestational age [inclusive]) or a full-term infant (born at over 35 weeks gestational age), as confirmed in medical records. * Weighs ≥2 kg at screening.

Health status

Negative to : HIV, HBV, HCV
Other health status: Participants must not have had prior known or documented RSV infection.

Study type

Interventional (clinical trial)

Enrollment

183

Allocation

Randomized

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Triple-blind masking

Masking description

Triple (Participant, Care Provider, Investigator)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intramuscular

Use case

Prevention

Key results

Type of key results	Title	Website link
Article	A Phase 1b/2a Single Ascending Dose Study of a Half-life Extended RSV Neutralizing Antibody, Clesrovimab, in Healthy Preterm and Full-term Infants	https://doi.org/10.1093/infdis/jiae581
Article	Development of High-Titer Antidrug Antibodies in a Phase 1b/2a Infant Clesrovimab Trial Are Associated With RSV Exposure Beyond Day 150	https://doi.org/10.1093/infdis/jiae582

SMART

Identifier

NCT04938830

Link

https://clinicaltrials.gov/study/NCT04938830

Phase

Phase III

Status

Active, not recruiting

Sponsor

Merck Sharp & Dohme LLC

More details

This study aims to evaluate the safety and tolerability of clesrovimab compared to palivizumab as assessed by the proportion of participants experiencing adverse events (AEs).

Purpose

Clesrovimab (MK-1654) in Infants and Children at Increased Risk for Severe Respiratory Syncytial Virus (RSV) Disease (MK-1654-007)

Interventions

Intervention 1

Biological: Clesrovimab IM injection

Intervention 2

Biological: Palivizumab IM injection

Intervention 3

Biological: Placebo IM injection

Countries

Australia

Canada

Chile

Colombia

Czechia

Finland

France

Germany

Greece

Hong Kong

Hungary

Italy

Japan

Malaysia

Mexico

New Zealand

Norway

Peru

Puerto Rico

Singapore

South Africa

Spain

Taiwan, Province of China

Thailand

Türkiye

United Kingdom

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-11-30

Anticipated Date of Last Follow-up

2025-03-17

Estimated Primary Completion Date

2025-04-29

Estimated Completion Date

2025-08-13

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Children

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria: * Participants at increased risk for severe RSV infection recommended to receive palivizumab in accordance with national or local guidelines or professional society recommendations. * Is available to complete the follow-up period. Exclusion Criteria: * Requires mechanical ventilation at time of enrollment. * Has a life expectancy <6 months. * Has known hepatic or renal dysfunction, or chronic seizure disorder. * Is hospitalized at the time of randomization unless discharge is expected within 7 days after randomization. * Has severe immunodeficiency or is severely immunocompromised. * Has known hypersensitivity to any component of clesrovimab or palivizumab.

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

1000

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Triple-blind masking

Masking description

Triple (Participant, Care Provider, Investigator)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intramuscular

Use case

Prevention

Key results

Not provided

MK-1654-005

Identifier

NCT04086472

Link

https://clinicaltrials.gov/study/NCT04086472

Phase

Phase II

Status

Completed

Sponsor

Merck Sharp & Dohme LLC

More details

The primary objective of this study is to determine if a single intravenous (IV) dose of clesrovimab when administered at 1 of 4 dose levels results in a reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to IV placebo. It is hypothesized that at least 1 of the 4 dose levels of clesrovimab given prior to inoculation will reduce the area under the viral load-time curve (VL-AUC) from Day 2 through Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40) compared to placebo.

Purpose

Phase 2a Respiratory Syncytial Virus (RSV) Human Challenge Study of Clesrovimab (MK-1654) in Healthy Participants (MK-1654-005)

Interventions

Intervention 1

Biological: Clesrovimab

Dosage: 100 mg, 200 mg, 300 mg or 900 mg

Intervention 2

Placebo Comparator: Placebo

Countries

United Kingdom

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2019-10-28

Anticipated Date of Last Follow-up

2022-08-29

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2020-03-22

Actual Completion Date

2020-08-14

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Inclusion Criteria: * Is a male or female 18 to 55 years of age in good health with no history of major medical conditions that will interfere with participant safety, as defined by medical history, physical examination (including vital signs), electrocardiogram (ECG), and routine laboratory tests and determined by the Investigator at a screening evaluation. * Has a total body weight ≥ 50 kg and Body Mass Index (BMI) ≥ 18 kg/m\^2 and ≤ 30kg/m\^2. * If male, agrees to study contraceptive requirements at dosing and continuing until 90 days after dosing or 28 days after viral inoculation (whichever is later) and to not donate sperm until 90 days after dosing. * If female, has a negative pregnancy test at screening and prior to dosing and agrees to use one form of effective contraception.

Health status

Negative to : HIV, HCV, HBV

Study type

Interventional (clinical trial)

Enrollment

80

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Triple-blind masking

Masking description

Triple (Participant, Investigator, Outcomes Assessor)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Prevention

Key results

Type of key results	Title	Website link
Article	Forward and reverse translational approaches to predict efficacy of neutralizing respiratory syncytial virus (RSV) antibody prophylaxis	https://doi.org/10.1016/j.ebiom.2021.10

Excipients

Proprietary excipients used

No proprietary excipient used

Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

No novel excipient or existing excipient used

Residual solvents used

No residual solvent used

Patent info

Compound patent families

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Clesrovimab Expiry date: 2036-10-27 The present invention relates to monoclonal antibodies which have high anti-RSV neutralizing titers. The invention further provides for isolated nucleic acids encoding the antibodies of the invention and host cells transformed therewith. The invention yet further provides for diagnostic, prophylactic and therapeutic methods employing the antibodies and nucleic acids of the invention, particularly as a passive immunotherapy agent in infants and the elderly.	WO2017075124	Compound	Merck Sharp & Dohme Corp	No	

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	China, Mexico, South Africa, India, Namibia, Ghana, Botswana, Kenya, Colombia, Costa Rica, Indonesia, Mongolia, Nigeria	Australia, Chile, Japan, Korea, Republic of, United States of America, Panama, Seychelles
Filed	Argentina, Brazil, Tajikistan, Belarus, Azerbaijan, Turkmenistan, Armenia, Kyrgyzstan, Kazakhstan, Ecuador, Morocco, Albania, Serbia, Bosnia and Herzegovina, Montenegro, Türkiye, Moldova, Republic of, North Macedonia, Georgia, Jordan, Malaysia, Nicaragua, Peru, Philippines, El Salvador, Tunisia, Ukraine, Dominican Republic, Egypt, Guatemala, Honduras, Iran (Islamic Republic of), Jamaica, Lebanon, Sri Lanka, Thailand, Pakistan	Australia, Canada, Russian Federation, Liechtenstein, Italy, Norway, Malta, Denmark, Belgium, United Kingdom, Greece, Netherlands, Hungary, Croatia, Switzerland, Spain, San Marino, Slovenia, Austria, Romania, Iceland, Cyprus, Finland, France, Bulgaria, Slovakia, Poland, Latvia, Ireland, Estonia, Germany, Luxembourg, Portugal, Czechia, Lithuania, Monaco, Sweden, Hong Kong, Israel, Singapore, Taiwan, Province of China, United States of America, Brunei Darussalam, Kuwait, United Arab Emirates, Bahrain, Saudi Arabia, Oman, Qatar, New Zealand, Trinidad and Tobago

Patent status/countries	Low, Low- middle and upper-middle	High income
Not in force	World Intellectual Property Organization (WIPO), Sierra Leone, Eswatini, Liberia, Sao Tome and Principe, Mozambique, Uganda, Zambia, Zimbabwe, Tanzania, United Republic of, Malawi, Rwanda, Sudan, Lesotho, Gambia (the)	World Intellectual Property Organization (WIPO), Australia

Supporting material

Publications

Phuah JY, Maas BM, Tang A, Zhang Y, Caro L, Railkar RA, Swanson MD, Cao Y, Li H, Roadcap B, Catchpole AP, Aliprantis AO, Vora KA. Quantification of clesrovimab, an investigational, half-life extended, anti-respiratory syncytial virus protein F human monoclonal antibody in the nasal epithelial lining fluid of healthy adults. Biomed Pharmacother. 2023 Dec 31;169:115851. DOI: 10.1016/j.biopha.2023.115851. Epub 2023 Nov 14. PMID: 37976891.

Background: Clesrovimab (MK-1654) is an investigational, half-life extended human monoclonal antibody (mAb) against RSV F glycoprotein in clinical trials as a prophylactic agent against RSV infection for infants.

Methods: This adult study measured clesrovimab concentrations in the serum and nasal epithelial lining fluid (ELF) to establish the partitioning of the antibody after dosing. Clesrovimab concentrations in the nasal ELF were normalized for sampling dilution using urea concentrations from ELF and serum. Furthermore, in vitro RSV neutralization of human nasal ELF following dosing was also measured to examine the activity of clesrovimab in the nasal compartment.

Findings: mAbs with YTE mutations are reported in literature to partition ~1-2 % of serum antibodies into nasal mucosa. Nasal: serum ratios of 1:69-1:30 were observed for clesrovimab in two separate adult human trials after urea normalization, translating to 1.4-3.3 % of serum concentrations. The nasal PK and estimates of peripheral volume of distribution correlated with higher extravascular distribution of clesrovimab. These higher concentration of the antibody in the nasal ELF corroborated with the nasal sample's ability to neutralize RSV ex vivo. An overall trend of decreased viral plaque AUC was also noted with increasing availability of clesrovimab in the nasal ELF from a human RSV challenge study.

Interpretation: Along with its extended half-life, the higher penetration of clesrovimab into the nasal epithelial lining fluid and the associated local increase in RSV neutralization activity could offer infants better protection against RSV infection.

Keywords: Monoclonal antibody; Nasal epithelial lining fluid; RSV; Respiratory syncytial virus; Urea normalization.

Additional documents

No documents were uploaded

Useful links

- Clesrovimab (MK-1654): Pediatric Clinical Program
- Merck’s Clesrovimab (MK-1654), an Investigational Respiratory Syncytial Virus (RSV) Preventative

Access principles

Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

Work with MPP to expand access in LMICs

In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

Comment & Information

Not provided