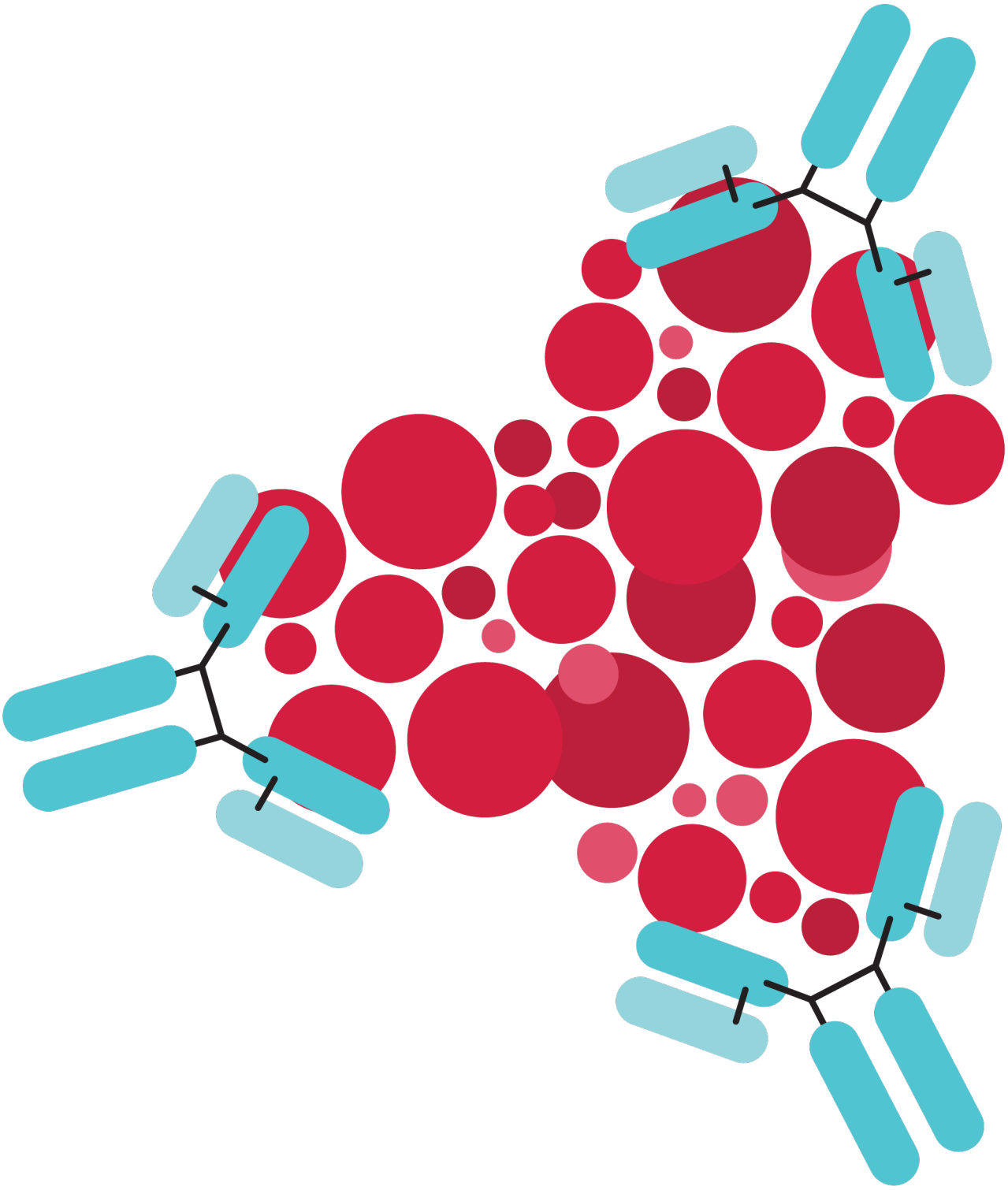


# Therapeutics for Ebola virus disease

19 August 2022

World Health Organization

# Therapeutics for Ebola virus disease

19 August 2022

World Health Organization

Therapeutics for Ebola virus disease, 19 August 2022

ISBN 978-92-4-005574-2 (electronic version)
ISBN 978-92-4-005575-9 (print version)



**Suggested citation.** Therapeutics for Ebola virus disease, 19 August 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at http://apps.who.int/iris.

**Sales, rights and licensing.** To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see https://www.who.int/copyright.



Design and layout: L'IV Com Sàrl

# Contents

# Acknowledgements

The World Health Organization (WHO) would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent.

**Clinical Co-Chairs:** Richard Kojan (ALIMA, Democratic Republic of the Congo); Robert Fowler (University of Toronto, Canada).

**Methods Chair:** Gordon Guyatt (McMaster University, Canada).

**Guideline Development Group (GDG) members:** Aasim Ahmad (National Bioethics Committee, Pakistan); Cindy Albertson (Samaritan's Purse, United States of America (USA)); Séverine Caluwaerts (Médecins Sans Frontières, Belgium); A Modet Camara (ALIMA, Guinea); Ian Crozier (Frederick National Laboratory, USA); Hilde De Clerck (Médecins Sans Frontières, Belgium); Susanna Dunachie (University of Oxford, United Kingdom of Great Britain and Northern Ireland (United Kingdom)); William A Fischer (University of North Carolina, USA); Bushra Jamil (Aga Khan University, Pakistan); Patricia Kabuni (Kinshasa University Clinic, Democratic Republic of the Congo); Charline Kahambu Ngorombi (Ministry of Health, Democratic Republic of the Congo); Maurice Kakule (Mangodomu Reference Health Centre, Democratic Republic of the Congo); Marie-Claire Kolié (ALIMA, Guinea); Sulaiman Lakoh (Ministry of Health and Sanitation, Sierra Leone); Hans-Jörg Lang (ALIMA, Germany); J Soka Moses (Ministry of Health, Liberia); Isekusu Mpinda Fiston (Ministry of Health, Democratic Republic of the Congo); Philippe Mukumbayi Mulumba (Institut National de Recherche Biomédicale, Democratic Republic of the Congo); Srinivas Murthy (University of British Columbia, Canada); Sorie Samura (National Emergency Medical Services, Sierra Leone).

A list of GDG members with accompanying biographies can be found on the WHO Health Care Readiness and Clinical Unit website: WHO Guideline Development Group for Therapeutics for Ebola Virus Disease[1].

**Systematic review team:** Rachel Couban (McMaster University, Canada); Ya Gao (Lanzhou University, China); Long Ge (Lanzhou University, China); Qiukui Hao (McMaster University, Canada); Jinhui Tian (Lanzhou University, China); Yunli Zhao (West China Hospital, Sichuan University, China).

**Guideline core GRADE[2] team:** The guideline core GRADE team reviewed the systematic review and GRADE tables and prepared materials for the GDG and wrote the final guideline. Lisa Askie (Scientist, Methods Lead, Methods and Standards Team, Quality Assurance Norms and Standards, Science Division, WHO); Janet Diaz (Lead, Clinical Management, Health Care Readiness, Geneva, WHO); Robert Fowler; Gordon Guyatt; Qiukui Hao; Richard Kojan; Marta Lado (Clinical Management, Health Care Readiness, Geneva, WHO); Daniel Youkee (Clinical Management, Health Care Readiness, Geneva, WHO).

**WHO Steering Committee:** Julienne Anoko (Focal Point, Risk Communication and Community Engagement, WHO Regional Desk for Health Emergencies, Dakar); Lisa Askie; Mercedes Bonet (Sexual and Reproductive Health and Research, Geneva, WHO); Alejandro Javier Costa (Health Emergencies Operations, Geneva, WHO); Vanessa Cramond (Clinical Management, Health Care

[1] https://www.who.int/publications/m/item/who-global-guideline-development-group-for-therapeutics-for-ebola-virus-disease

[2] Grading of Recommendations Assessment, Development and Evaluation.

Readiness, Geneva, WHO); Janet Diaz; Luca Fontana (Health Emergencies Operations, Geneva, WHO); Pierre Formenty (Team Lead, Viral Haemorrhagic Fevers; Health Emergency Interventions, Health Emergencies Programme, Geneva); Patrice Kabongo (Case Management, WHO African Region); Rashidatu Fouad Kamara (Case Management Lead, WHO African Region); Krutika Kuppalli (Clinical Management, Health Care Readiness, Geneva, WHO); Marta Lado; Lorenzo Moja (Essential Medicines List, Geneva, WHO); Maurice Nzogu (Clinical Management, Health Care Readiness, Geneva, WHO); Andreas Reis (Health Ethics and Governance Unit, Geneva, WHO); Pryanka Relan (Clinical Management, Health Care Readiness, Geneva, WHO); Julie Viry (Clinical Management, Health Care Readiness, Geneva, WHO); Victoria Willet (Infection Prevention and Control, Health Care Readiness, Geneva, WHO); Daniel Youkee.

**External reviewers:** Lori Dodd (National Institutes of Health, USA); Tom Fletcher (Liverpool School of Tropical Medicine, United Kingdom); Sabue Mulangu (Institut National de Recherche Biomédicale, Democratic Republic of the Congo); Jerome Pfaffman (United Nations Children's Fund). Professor Andrew Owen (University of Liverpool, United Kingdom) reviewed the mechanism of action sections for the four therapeutics.

WHO selected GDG members to ensure global geographical representation, gender balance, appropriate technical and clinical expertise and patient representation. The technical unit collected and managed declarations of interests (DOIs). In addition to the distribution of a DOI form, during the meeting, the WHO Secretariat described the DOI process and provided an opportunity for GDG members to declare any interests not provided in written form. Web searches did not identify any additional interests that could be perceived to affect an individual's objectivity and independence during the development of the recommendations. No GDG member was judged to have a significant conflict of interest.

**Funding source:** This guideline was funded with Unitaid funds.

# Abbreviations

| | |
|---|---|
| **Anti-IL-6** | anti-interleukin-6 |
| **Anti-TNF** | anti-tumor necrosis factor |
| **ALT/AST** | alanine aminotransferase/aspartate aminotransferase |
| **CI** | confidence interval |
| **CFR** | case fatality rate |
| **CT value** | cycle threshold value |
| **DOI** | declaration of interests |
| **EBOV** | Ebola virus |
| **EOI** | Expression of Interest |
| **EVD** | Ebola virus disease |
| **GDG** | Guideline Development Group |
| **GRC** | Guideline Review Committee |
| **GRADE** | Grading of Recommendations Assessment, Development and Evaluation |
| **HIV** | human immunodeficiency virus |
| **ICEMAN** | Instrument to assess the Credibility of Effect Modification Analyses |
| **IL-6** | interleukin-6 |
| **NMA** | network meta-analysis |
| **NP** | nucleoprotein |
| **PALM** | Pamoja Tulinde Maisha (Together Save Lives) (in Kiswahili) |
| **PICO** | population, intervention, comparator, outcomes |
| **RBD** | receptor binding domain |
| **RCT** | randomized controlled trial |
| **RT-PCR** | real-time polymerase chain reaction |
| **SD** | standard deviation |
| **WHO** | World Health Organization |

# Executive summary

**Clinical question:** What is the role of virus-specific therapeutics in the treatment of patients with Ebola virus disease (EVD), caused by Ebola virus (EBOV; Zaire ebolavirus)?

**Context:** The limited evidence base for therapeutics for EVD was augmented by the publication of the Pamoja Tulinde Maisha (PALM) randomized controlled trial (RCT) in 2019, which compared ZMapp with three investigational agents: remdesivir, REGN-EB3 and mAb114. This guideline reviews the existing evidence and provides recommendations for use of EBOV-specific therapeutics in patients with EVD.

**Target audience:** Health care providers caring for patients with EVD and policy-makers involved in EVD preparedness and response.

**Methods:** A systematic review and meta-analysis of RCTs of therapeutics for EVD was conducted. Recommendations based on the synthesized evidence were made by the GDG using GRADE methodology.

**New recommendations:** The GDG made the following recommendations:

- **Strong recommendation for** treatment with mAb114 or REGN-EB3 for patients with real-time polymerase chain reaction (RT-PCR) confirmed EVD **and** for neonates of unconfirmed EVD status, 7 days or younger, born to mothers with confirmed EVD;
- **Conditional recommendation against** treatment with remdesivir for patients with RT-PCR confirmed EVD;
- **Conditional recommendation against** treatment with ZMapp for patients with RT-PCR confirmed EVD.

**Availability:** Access to these therapeutics is challenging and pricing and future supply remain unknown, especially in resource-poor areas. Without concerted effort, access will remain limited, and it is therefore possible that this strong recommendation could exacerbate health inequity. Therefore, given the demonstrated benefits for patients, these recommendations should act as a stimulus to engage all possible mechanisms to improve global access to these treatments.

**About this guideline:** This guideline from WHO incorporates the latest high-quality evidence and provides new recommendations on EBOV-specific therapeutics for EVD. The GDG typically evaluates a drug when WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual patient perspective in making recommendations, it also considers resources implications, acceptability, feasibility, equity and human rights. This guideline was developed according to standards and methods for trustworthy guidelines.

**Nomenclature:** To facilitate comprehension, this guideline maintained the therapeutic names as they were described in the relevant RCTs and other peer-reviewed publications.

| Name used in RCTs | mAb114 | REGN-EB3 | remdesivir | ZMapp |
|---|---|---|---|---|
| **Molecular name** | ansuvimab | atoltivimab, maftivimab, and odesivimab-ebgn | remdesivir | 2G4, 4G7, 13C6 |
| **Commercial name** | Ebanga™ | Inmazeb™ | Veklury™ | ZMapp™ |

# 1. Introduction

Ebola virus disease (EVD) is a life-threatening disease caused by Ebola virus (EBOV; Zaire ebolavirus). Viruses of the genus *Ebolavirus* (of the family *Filoviridae*) can cause life-threatening disease. To date, six filoviruses have been discovered in humans, four in the genus *Ebolavirus* (Bundibugyo virus, EBOV, Sudan virus and Taï Forest virus) *(1)*. The remaining two human filoviruses belong to the genus *Marburgvirus* (Marburg virus and Ravn virus). EBOV causes outbreaks of EVD, historically the most severe and most frequent *(2)*. This guidance, due to the evidence available, is directed only to the treatment of EVD, the disease caused by EBOV (Zaire ebolavirus).

During early EVD, patients present with a non-specific febrile illness, followed by gastrointestinal signs and symptoms that frequently lead to hypovolaemia, metabolic acidosis, hypoglycaemia and multi-organ failure *(2)*. EVD case fatality remains high, with a pooled case fatality rate (CFR) of 60% (95% confidence interval (CI): 47–73%) in outbreaks from 2010–2020 *(3)*. In recent years, several outbreaks of EVD have occurred in Africa; including the prolonged 2013–2016 EVD outbreak in West Africa; the 2018–20, 2020, 2021 outbreaks in the Democratic Republic of the Congo; and the 2021 outbreak in Guinea *(4)*.

Following the publication of an RCT demonstrating superior efficacy of two EVD therapeutics, in comparison with the ZMapp control arm *(5)*, WHO proposed to develop a new guideline. This is a new guideline written to accompany the optimized supportive care for EVD standard operating procedures *(6, 7)*. This guideline aims to summarize high-quality evidence for EVD therapeutics and make recommendations for their use.

# 2. Methods: how this guideline was created

This WHO guideline was developed according to standards and methods for trustworthy guidelines, aligned with the *WHO Handbook for guideline development*, 2nd edition *(8)*, and according to a pre-approved protocol by the Guideline Review Committee (GRC). The guideline development process utilized the GRADE methodology *(9)*.

## Step 1: Convening the Therapeutics for Ebola virus disease Guideline Development Group

WHO selected GDG members to ensure global geographical representation, gender balance, appropriate technical and clinical expertise, and patient representation. The technical unit collected and managed DOIs. In addition to the distribution of a DOI form, during the meeting, the WHO Secretariat described the DOI process and provided an opportunity for GDG members to declare any interests not provided in written form. Web searches did not identify any additional interests that could be perceived to affect an individual's objectivity and independence during the development of the recommendations. No GDG member was judged to have a significant conflict of interest.

Biographies of GDG members were posted on 10 November 2021 and can be found online[3].

The pre-selected expert GDG convened on two occasions: the first meeting, held on 17 November 2021, introduced the members of the GDG to the WHO guideline development process and explained GRADE methodology. The GDG was tasked to review and finalize the research question (population, intervention, comparator, outcomes (PICO)); decide on which possible population subgroup hypotheses to explore; select therapeutic interventions of interest; consider variation in the standard of care comparator; and prioritize patient important outcomes. The GDG agreed to only consider RCT-level evidence in the evidence synthesis. A full report of the first GDG meeting can be found online *(10)*.

## Step 2: Finalizing the research question (population, intervention, comparator, and outcomes)

### Population

The GDG agreed that the overarching population would be all patients with RT-PCR confirmed EVD.

The GDG specified population subgroups of interest (see Table 1). The number of subgroups was limited to a maximum of five to avoid undermining the credibility of any apparent subgroup effect detected. Analyses addressed only subgroups with a clear pre-specified direction of effect. The table shows the pre-specified risk of mortality and the postulated direction of the effect.

[3] https://www.who.int/publications/m/item/who-global-guideline-development-group-for-therapeutics-for-ebola-virus-disease

**Table 1. Population subgroups and pre-specified direction of effect**

| Subgroups | Categories | Risk of mortality by category | Postulated direction of effect |
|---|---|---|---|
| **Age** | Paediatric/adult/older age<br>≤ 5 years, 5–59 years, ≥ 60 years | Paediatric and older age = higher risk of mortality | Paediatric and older age = reduced treatment effect |
| **Prior EVD vaccination** | Vaccination within 10 days,<br>> 10 days | Vaccination within 10 days = higher risk of mortality | Vaccination within 10 days = reduced treatment effect |
| **Day of illness (duration of symptoms prior to treatment)** | ≤ 5 days, > 5 days | Longer duration of illness (> 5 days) = higher risk of mortality | Duration > 5 days = reduced treatment effect |
| **Pregnancy** | Per trimester | Pregnancy = higher risk of mortality | Pregnancy = reduced treatment effect |
| **Disease severity as specified by GDG** | EVD-nucleoprotein (NP) value as proxy for viraemia<br>Creatinine<br>Liver function (AST/ALT) | Higher disease severity = higher risk of mortality<br>Lower EVD-NP CT value < 22 = higher risk of mortality | More severe disease = reduced treatment effect |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: cycle threshold.

### Intervention

The GDG suggested the following therapeutics to be included in the research question: antiviral agents, neutralizing monoclonal antibodies, convalescent plasma, anti-inflammatories, corticosteroids, anti-tumor necrosis factor (anti-TNF), interleukin-6 (IL-6) receptor blockers, blood products, endothelial stabilization agents (Fx06), interferon, antimalarials and antifibrinolytics.

### Comparator

The GDG acknowledged large heterogeneity in the standard of care and CFR for EVD by location, between outbreaks, and over time. This limitation was noted and is discussed in the limitations section (Section 5). Acknowledging the heterogeneity in available standard of care and in the related CFR of EVD outbreaks, the Steering Committee included two baseline risk estimates for mortality in the network meta-analysis (NMA). The group utilized the lowest and highest CFRs in outbreaks with no fewer than 100 diagnosed cases since 2013 reported by WHO *(11)*. The lowest baseline risk estimate of 39.5% CFR was derived from the 2013–2016, West African EVD outbreak and the highest baseline risk estimate of 66% CFR was derived from the 2018–2020 Democratic Republic of the Congo and Uganda outbreak.

### Outcomes

The GDG developed a list of 13 outcomes of interest to patients, families and health care providers. Outcomes were then prioritized through an online survey. The online survey was sent to 38 participants of the WHO Steering Committee and GDG members. The survey was also sent to five recovered EVD patients in Sierra Leone and five recovered EVD patients in the Democratic Republic of the Congo. Participants rated each outcome from 1 to 9: 7 to 9 as critically important, 4 to 6 as important, and 1 to 3 as of limited importance. The survey was provided in both French and English.

### Outcome prioritization results

A total of 25/38 (66%) GDG and WHO Steering Committee members completed the survey, and 10/10 (100%) of EVD patients completed the survey. There were no partial or incomplete responses, and no apparent evidence of scale inversion. Survey results were compiled centrally, the results are displayed as mean (standard deviation) in Table 2.

Four outcomes were ranked in the top five by both the GDG and WHO Steering Committee and EVD patients: mortality, adverse maternal outcomes, duration of admission and risk of onward transmission. The GDG included serious adverse effects in their top five, whilst EVD patients included functional status post-EVD. EVD patients reported higher overall mean prioritization scores than GDG members. All outcomes with a score ≥ 6.5 as ranked by all participants were included in the systematic review search strategy.

**Table 2. Outcome prioritization scores of GDG participants and EVD patients**

| Outcome | All respondents n=35, mean (SD) | GDG and WHO Steering Committee n=25, mean (SD) | EVD patients n=10, mean (SD) | All rank | GDG rank | EVD patients rank |
|---|---|---|---|---|---|---|
| **Duration of admission** | 7.3 (1.7) | 7.08 (1.7) | 7.6 (1.6) | 4 | 4 | 5 |
| **Mortality** | 8.7 (0.9) | 8.8 (0.5) | 8.2 (1.4) | 1 | 1 | 1 |
| **Time to symptom resolution** | 6.8 (1.8) | 6.8 (1.9) | 6.8 (1.6) | 8 | 7 | 11 |
| **Serious adverse effects** | 7.1 (1.7) | 7.2 (1.3) | 7.0 (2.5) | 6 | 3 | 10 |
| **Adverse maternal outcomes** | 7.5 (1.5) | 7.4 (1.2) | 7.6 (2.1) | 2 | 2 | 4 |
| **Time to viral clearance** | 6.5 (2.1) | 6.4 (1.9) | 6.8 (2.7) | 9 | 9 | 12 |
| **Mental health outcomes** | 6.4 (1.8) | 6.0 (1.4) | 7.2 (2.6) | 10 | 10 | 8 |
| **Adverse perinatal outcomes** | 6.9 (1.7) | 6.8 (1.5) | 7.2 (2.4) | 7 | 8 | 7 |
| **Interruption of treatment** | 5.9 (2.6) | 5.8 (2.6) | 6 (2.7) | 13 | 12 | 13 |
| **Viraemia through disease course** | 6.3 (2.7) | 5.8 (2.7) | 7.5 (2.4) | 12 | 13 | 6 |
| **Functional status post EVD** | 7.2 (1.6) | 6.8 (1.6) | 8.1 (1.5) | 5 | 6 | 3 |
| **Risk of onward transmission** | 7.3 (2.0) | 6.9 (1.9) | 8.2 (1.9) | 3 | 5 | 2 |
| **Future fertility outcomes** | 6.3 (2.1) | 6.0 (1.9) | 7.1 (2.3) | 11 | 11 | 9 |
| **Mean outcome prioritization score** | 6.93 (2.0) | 6.78 (1.9) | 7.3 (2.2) | — | — | — |

These steps led to the generation of a final PICO, displayed in Table 3.

**Table 3. Final research question (PICO)**

| | |
|---|---|
| **Population** | **All patients with confirmed EVD of any disease severity** |
| **Intervention** | Antiviral agents, neutralizing monoclonal antibodies, convalescent plasma.<br>Anti-inflammatories, corticosteroids, anti-TNF, IL-6 receptor blockers, blood products, endothelial stabilization agents (Fx06), interferon, antimalarials, antifibrinolytics. |
| **Comparator** | Standard care |
| **Outcomes** | Mortality, adverse maternal outcomes, duration of admission, risk of onward transmission, serious adverse effects, functional status post EVD, adverse perinatal outcomes, time to symptom resolution, time to viral clearance. |
| **Potential subgroups of interest** | 1. Age ≤ 5 years, 6–17 years, 18–59 years, ≥ 60 years<br>2. Prior EVD vaccination<br>3. Disease severity (CT value ≤ 22 vs > 22)<br>4. Pregnancy<br>5. Day of illness on admission |

## Step 3: Evidence synthesis and GRADE

Based on the final PICO in Table 3, the systematic review team, as requested by the GDG, performed an independent systematic review. The systematic review team included systematic review experts, clinical experts, clinical epidemiologists and biostatisticians. Team members had expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The systematic review team considered deliberations from the initial GDG meeting, specifically focusing on the outcomes and subgroups prioritized by the GDG. The methods team rated credibility of subgroups using the ICEMAN tool *(12)*. The systematic review methods and results are published in *Lancet Microbe* DOI: https://doi.org/10.1016/S2666-5247(22)00123-9 *(13)*. From the meta-analysis results summary of the evidence was GRADED with the WHO core EVD Steering Committee, clinical co-chairs and GDG methodologist. The following criteria were used to standardize the GRADE process:

- Certainty of the evidence was rated according to an effect greater or less than the minimally important difference. These were determined as:
  - **Mortality:** 10 per 1000
  - **Serious adverse events:** 20 per 1000
  - **Time to viral clearance:** 1 day
  - **Duration of admission:** 1 day.
- Certainty of the evidence was rated down 1 level for imprecision if the 95% CI lower limit *or* higher limit crossed the threshold.
- Certainty of the evidence was rated down 2 levels for imprecision if the 95% CI lower limit *and* higher limit *both* crossed the threshold of both important harm and important benefit.
- Certainty of the evidence was rated down 3 levels for imprecision if 95% CI included both large benefit and large harm.

The 95% CIs were described as wide when they span a clearly important effect and an effect that is substantially less or not important. The 95% CIs were described as very wide when they include a large effect and minimal or no effect, or when they include important benefit and important harm. The 95% CIs were described as extremely wide when they include large benefit and moderate or large harm, or large harm and moderate or large benefit.

## Step 4: Final recommendations

The second expert GDG meeting was held on 23 February 2022 and focused on reviewing the evidence and deciding on recommendations. The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(9, 14)*. If the GDG members had disagreed regarding the evidence assessment or strength of recommendations, the panel chairs would have applied established WHO voting rules *(14, 15)*. This proved unnecessary; there was no voting and all decisions were made by consensus.

The following key factors informed transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) *(16);*
- quality/certainty of the evidence *(9, 17);*
- values and preferences of patients *(15);*
- resources and other considerations (including considerations of feasibility, applicability and equity) *(15);*
- effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence, as presented in summary of findings tables. If such data are not available, the GDG reviews narrative summaries *(16);*
- recommendations are rated as either conditional or strong, as defined by GRADE.

# 3. Recommendations

## Results of the systematic review

The full results of the search strategy and the protocol can be found here DOI: https://doi.org/10.1016/S2666-5247(22)00123-9 *(13)*. Two RCTs were found which met the inclusion criteria. PREVAIL II published by Davey et al. in 2016 *(18)*, and the PALM trial published by Mulangu et al. in 2019 *(5)*. The two trials investigated four therapeutics, ZMapp (a triple monoclonal antibody agent), remdesivir (a nucleotide analogue RNA polymerase inhibitor), mAb114 (a single human monoclonal antibody derived from an Ebola survivor) and REGN-EB3 (a coformulated mixture of three IgG1 monoclonal antibodies).

**PREVAIL II**

PREVAIL II was an RCT of ZMapp vs standard of care. Patients were stratified according to baseline EBOV-NP PCR CT value for the virus (≤ 22 vs > 22) and country of enrolment. Patients of any age were enrolled. No pregnant women were recruited in this trial. The primary endpoint was 28-day mortality. A total of 72 patients (36 per group) were enrolled at multiple sites, two in Liberia, seven in Sierra Leone, one in Guinea, and one in the United States of America, from March to November 2015. Of the 71 patients who could be evaluated, 21 died, representing an overall CFR of 30%. Death occurred in 13 of 35 patients who received the current standard of care alone, and in 8 of 36 patients who also received ZMapp.

**PALM**

PALM, was a randomized trial of ZMapp vs three other EBOV-specific therapeutics, conducted in the Democratic Republic of the Congo in 2018 to 2019. Patients were assigned in a 1:1:1:1 ratio to receive ZMapp, remdesivir, mAb114, or REGN-EB3. Patients of any age, including pregnant women, were eligible if they had a positive result on RT-PCR. Neonates < 7 days of unconfirmed EVD status were also eligible if they were born to a mother with documented EVD. Patients were stratified according to baseline PCR CT value for the virus (≤ 22 vs > 22). The primary end-point was 28-day mortality. A total of 681 patients were enrolled, from 20 November 2018 to 9 August 2019. At 28 days, death had occurred in 61 of 174 patients (35.1%) in the mAb114 group, as compared with 84 of 169 (49.7%) in the ZMapp group ($P = 0.007$), and in 52 of 155 (33.5%) in the REGN-EB3 group, as compared with 79 of 154 (51.3%) in the ZMapp subgroup ($P = 0.002$).

## 3.1 Recommendation for mAb114 and REGN-EB3

**Strong recommendation for**

We recommend treatment with either mAb114 or REGN-EB3 for patients with RT-PCR confirmed EVD **and** for neonates of unconfirmed EVD status, 7 days or younger, born to mothers with confirmed EVD (*strong recommendation for*).

**Remarks**

- mAb114 and REGN-EB3 should not be given together, and should be viewed as alternatives. The choice of whether to use mAb114 and REGN-EB3 depends on availability.
- This recommendation only applies to EVD caused by Ebola virus (EBOV; Zaire ebolavirus).

### Evidence to decision

**Benefits and harms**

mAb114 and REGN-EB3 probably reduce mortality compared with standard of care when using the lowest and the highest baseline risk estimates. Whether mAb114 and REGN-EB3 increase serious adverse events compared with standard of care is very uncertain. mAb114 and REGN-EB3 may have little or no effect on time to viral clearance.

**Subgroup effects**

No subgroup effects were found for mortality for mAb114 or REGN-EB3 vs standard of care by age group or CT value. Neither were subgroup effects found for mortality for mAb114 vs REGN-EB3 in a head-to-head comparison, by age group, CT value, self-reported prior EVD vaccination, or duration of symptoms at admission.

**Certainty of the evidence**

For the key outcome of mortality, the panel rated the evidence as moderate certainty. Due to the lack of a standard care arm in the PALM study, indirect comparisons for mAb114 and REGN-EB3 via the PREVAIL II study informed the estimate. The PREVAIL II study included only 71 participants, resulting in very wide CIs; this was the rationale for rating down certainty from high to moderate.

The high certainty evidence of the superiority of mAb114 and REGN-EB3 versus ZMapp and remdesivir and the low likelihood that both ZMapp and remdesivir increase mortality in EVD patients further support the inference of the beneficial effect of mAb114 and REGN-EB3.

Whether mAb114 and REGN-EB3 increase serious adverse events is very uncertain due to very serious imprecision with extremely wide CIs, and due to risk of bias generated by the unblinded design of the PALM RCT.

Due to very serious imprecision with wide CIs that include both benefit and harm, there is low certainty of evidence for any effect of mAb114 and REGN-EB3 on time to viral clearance.

**Values and preferences**

The panel inferred that all patients would place a very high value on the mortality reduction conferred by mAb114 and REGN-EB3.

**Resources and other considerations**

Access to these therapeutics is challenging (pricing and future supply remain unknown) in many parts of the world and, without concerted effort, is likely to remain so, especially in resource-poor areas. It is therefore possible that this strong recommendation could exacerbate health inequity. Therefore, given the demonstrated benefits for patients, it should also provide a stimulus to engage all possible mechanisms to improve global access to these treatments.

On 5 October 2021 the WHO Prequalification Unit published the 1st Invitation to Manufacturers of therapeutics against Ebola Virus Disease to submit an Expression of Interest (EOI) for Product Evaluation[4].

**Acceptability and feasibility**

Compared with remdesivir and ZMapp, mAb114 and REGN-EB3 are simpler to administer as a single dose via intravenous infusion, which is likely both acceptable to the patient and feasible to administer. In comparison with remdesivir, mAb114 and REGN-EB3 are easier to monitor, and do not require ongoing viral load monitoring.

Ensuring availability for mAb114 and REGN-EB3 should not be at the expense of providing optimized supportive care. In the PALM RCT recruitment only began once every study site could deliver the standard optimized supportive care to all participants. Therefore the therapeutics build upon the platform of optimized supportive care and are not a replacement or alternative to it.

## Justification

Due to very similar evidence profiles of mAb114 and REGN-EB3 versus standard of care, and low certainty evidence suggesting little or no difference between the two agents in mortality and serious side-effects in the head-to-head comparison, the GDG decided on a strong recommendation for both drugs without any expression of preference for one or the other.

Both mAb114 and REGN-EB3 likely have important reductions in mortality, the most important outcome for patients, relative to standard of care:

- The absolute benefit of mAb114 for mortality of between 229 and 383 fewer deaths per 1000 patients is an important reduction in mortality.
- The absolute benefit of REGN-EB3 for mortality of between 237 and 396 fewer deaths per 1000 patients is an important reduction in mortality.

The GDG decided to include neonates less than 7 days old, of unconfirmed EVD status, born to mothers with EVD in this recommendation. The GDG decided to maintain the eligibility criteria that were used in the PALM RCT with the underlying rationale that mother and neonate are a connected pair, that transmission to neonate is extremely likely, mortality in this group very high, and delaying treatment would be prejudicial to the neonate's health.

The dearth of evidence establishing any increase in serious adverse effects further supports the recommendation.

## Practical information

To maximize likelihood of therapeutic effect, mAb114 or REGN-EB3 should be administered as soon as possible after diagnosis.

---

[4] https://extranet.who.int/pqweb/news/1st-invitation-manufacturers-therapeutics-against-ebola-virus-disease-submit-expression

Both mAb114 and REGN-EB3 are given as a single dose by intravenous infusion. See Annexes 1 and 2.

mAb114 prescribing information

**Available formulation of mAb114**

A vial contains: 400 mg off-white to white lyophilized powder. Upon reconstitution, one vial contains 8 mL of solution, containing 50 mg/mL of mAb114.

**Dosage and route of mAb114**

The recommended dose of mAb114 for adult and paediatric patients is 50 mg/kg (or 1 mL/kg) reconstituted with Sterile Water for Injection, further diluted and administered as a single intravenous infusion over 60 minutes.

For detailed information on dosing, see Annex 1.

REGN-EB3 prescribing information

**Available formulation of REGN-EB3**

A vial of REGN-EB3 (14.5 mL) contains:

241.7 mg (16.67 mg per mL) of atoltivimab;
241.7 mg (16.67 mg per mL) of maftivimab; and
241.7 mg (16.67 mg per mL) of odesivimab.

**Dosage and route of REGN-EB3**

The recommended dosage of REGN-EB3 is 150 mg/kg (equivalent to 3 mL/kg):

50 mg of atoltivimab;
50 mg of maftivimab; and
50 mg of odesivimab.

per kg

diluted and administered as a single intravenous infusion over 2 to 4 hours depending on body weight.

For detailed information on dosing, see Annex 2.

**PICO**

Population: Patients with Ebola virus disease
Intervention: mAb114
Comparator: Standard care

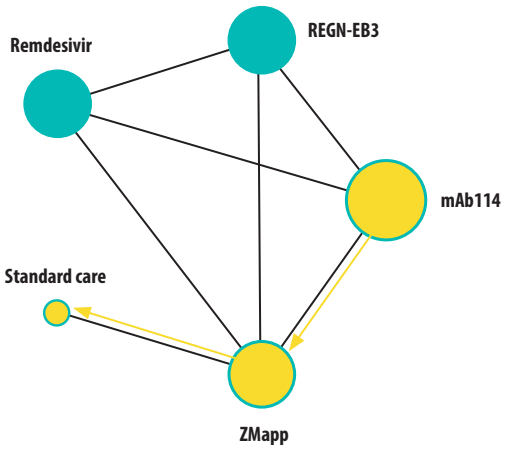
## Summary

**Evidence summary**

The evidence for mAb114 compared with standard care was informed by the PALM and PREVAIL II studies.

For patients with confirmed EVD, the GRADE summary of findings table (see Fig. 1) shows the relative and absolute effects of mAb114 compared with standard care for the outcomes of interest, with certainty ratings, informed by the systematic review. The network plot of the indirect comparison between mAb114 and standard care is shown below.

**Fig. 1 Network plot of indirect comparison of mAb114 compared with standard care via ZMapp**




| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Standard care | <br>mAb114 | Certainty of the evidence<br>(Quality of evidence) | Plain language summary |
|---|---|---|---|---|---|
| Mortality<br>(absolute effect estimated from lowest baseline risk) | Relative risk: 0.42<br>(CI 95% 0.19–0.93)<br>Follow up based on indirect evidence | **395**<br>per 1000 | **166**<br>per 1000<br>Difference: **229 fewer per 1000**<br>(CI 95% 320 fewer–28 fewer) | **Moderate**<br>Due to serious imprecision[a] | mAb114 probably reduces mortality compared with standard care when using the lowest baseline risk estimate. |
| Mortality<br>(absolute effect estimated from highest baseline risk) | Relative risk: 0.42<br>(CI 95% 0.19–0.93)<br>Follow up based on indirect evidence | **660**<br>per 1000 | **277**<br>per 1000<br>Difference: **383 fewer per 1000**<br>(CI 95% 535 fewer–46 fewer) | **Moderate**<br>Due to serious imprecision[b] | mAb114 probably reduces mortality compared with standard care when using the highest baseline risk estimate. |
| Serious adverse events | Risk difference: 0.016<br>(CI 95% 0.061–0.93)<br>Based on indirect evidence | Difference: **16.0 more per 1000**<br>(CI 95% 61.0 fewer–93.0 more) | | **Very low**<br>Due to serious risk of bias and very serious imprecision[c] | Whether mAb114 increases serious adverse events compared with standard care is very uncertain. |
| Time to viral clearance | Measured by days:<br>Scale: Lower better<br>Follow up based on indirect evidence | **8.68**<br>Mean | **7.54**<br>Mean<br>Difference: **MD 1.14 lower**<br>(CI 95% 4.09 lower–1.81 higher) | **Low**<br>Due to very serious imprecision[d] | mAb114 may have little or no effect on time to viral clearance compared with standard care. |

[a] **Imprecision: serious.** Small number of patients in the standard care versus ZMapp comparator informing this indirect comparison;
[b] **Imprecision: serious.** Small number of patients in the standard care versus ZMapp comparator informing this indirect comparison;
[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **imprecision: very serious**. Wide confidence intervals;
[d] **Imprecision: very serious.** Wide confidence intervals.

**PICO**

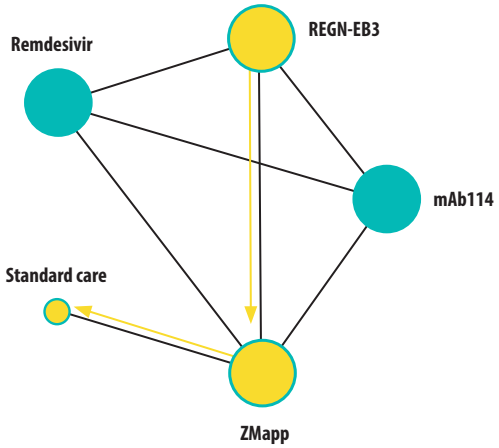
Population: Patients with Ebola virus disease
Intervention: REGN-EB3
Comparator: Standard care

## Summary

### Evidence summary

The evidence for REGN-EB3 compared with standard care was informed by the PALM and PREVAIL II studies. The indirect comparison of REGN-EB3 with standard care via ZMapp is shown below. For patients with confirmed EVD, the GRADE summary of findings table (see Fig. 2) shows the relative and absolute effects of REGN-EB3 compared with standard care for the outcomes of interest, with certainty ratings, informed by the systematic review. The network plot of the indirect comparison between REGN-EB3 and standard care is shown below.

**Fig. 2 Network plot of direct comparison of REGN-EB3 with standard care via ZMapp**




| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Standard care | <br>REGN-EB3 | Certainty of the evidence<br>(Quality of evidence) | Plain language summary |
|---|---|---|---|---|---|
| Mortality<br>(absolute effect estimated from lowest baseline risk) | Relative risk: 0.4<br>(CI 95% 0.18–0.89)<br>Follow up based on indirect evidence | **395**<br>per 1000 | **158**<br>per 1000<br>Difference: **237 fewer per 1000**<br>(CI 95% 324 fewer–43 fewer) | **Moderate**<br>Due to serious imprecision[a] | REGN-EB3 probably reduces mortality compared with standard care when using the lowest baseline risk estimate. |
| Mortality<br>(absolute effect estimated from highest baseline risk) | Relative risk: 0.4<br>(CI 95% 0.18–0.89)<br>Follow up based on indirect evidence | **660**<br>per 1000 | **264**<br>per 1000<br>Difference: **396 fewer per 1000**<br>(CI 95% 541 fewer–73 fewer) | **Moderate**<br>Due to serious imprecision[b] | REGN-EB3 probably reduces mortality compared with standard care when using the highest baseline risk estimate. |
| Serious adverse events | Risk difference: 0.016<br>(CI 95% 0.061–0.93)<br>Based on indirect evidence | Difference: **16.0 more per 1000**<br>(CI 95% 61.0 fewer–93.0 more) | | **Very low**<br>Due to serious risk of bias and very serious imprecision[c] | Whether REGN-EB3 increases serious adverse events compared with standard care is very uncertain. |
| Time to viral clearance | Measured by days:<br>Scale: Lower better<br>Follow up based on indirect evidence | **8.68**<br>Mean | **8.38**<br>Mean<br>Difference: **MD 0.30 lower**<br>(CI 95% 3.20 lower–2.60 higher) | **Low**<br>Due to very serious imprecision[d] | REGN-EB3 may have little or no effect on time to viral clearance compared with standard care. |

[a] **Imprecision: serious.** Small number of patients in the standard care versus ZMapp comparator informing this indirect comparison;
[b] **Imprecision: serious.** Small number of patients in the standard care versus ZMapp comparator informing this indirect comparison;
[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **imprecision: very serious**. Wide confidence intervals;
[d] **Imprecision: very serious.** Wide confidence intervals.

### PICO

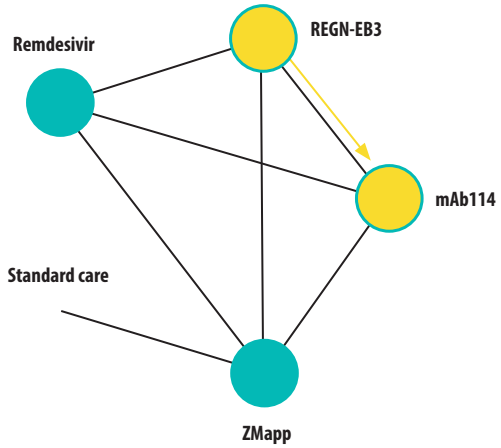
Population: Patients with Ebola virus disease
Intervention: REGN-EB3
Comparator: mAb114

## Summary

### Evidence summary

The evidence for REGN-EB3 compared with mAb114 is informed by the PALM study. The direct comparison of REGN-EB3 with mAb114 is shown below. For patients with confirmed EVD, the GRADE summary of findings table (see Fig. 3) shows the relative and absolute effects of REGN-EB3 compared with mAb114 for the outcomes of interest, with certainty ratings, informed by the systematic review. The network plot of the direct comparison between REGN-EB3 and mAb114 is shown below.

**Fig. 3 Network plot of direct comparison of REGN-EB3 to mAb114**




| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>mAb114 | <br>REGN-EB3 | Certainty of the evidence<br>(Quality of evidence) | Plain language summary |
|---|---|---|---|---|---|
| Mortality<br>(absolute effect estimated from lowest baseline risk) | Relative risk: 0.96<br>(CI 95% 0.71–1.29)<br>Based on data from 329 participants in 1 study | **166**<br>per 1000 | **159**<br>per 1000<br>Difference: **7 fewer per 1000**<br>(CI 95% 48 fewer–48 more) | **Low**<br>Due to very serious imprecision[a] | There may be little or no difference between REGN-EB3 and mAb114 when using the lowest baseline risk estimate. |
| Mortality<br>(absolute effect estimated from highest baseline risk) | Relative risk: 0.96<br>(CI 95% 0.71–1.29)<br>Based on data from 329 participants in 1 study | **277**<br>per 1000 | **266**<br>per 1000<br>Difference: **11 fewer per 1000**<br>(CI 95% 80 fewer–80 more) | **Low**<br>Due to very serious imprecision[b] | There may be little or no difference between REGN-EB3 and mAb114 when using the highest baseline risk estimate. |
| Serious adverse events | Risk difference: 0.000<br>(CI 95% 0.012–0.012)<br>Based on data from 329 participants in 1 study | Difference: **0.0 fewer per 1000**<br>(CI 95% 12.0 fewer–12.0 more) | | **Moderate**<br>Due to serious risk of bias[c] | There is probably little or no difference between REGN-EB3 and mAb114 in serious adverse events. |
| Time to viral clearance | Measured by days:<br>Scale: Lower better<br>Based on data from 216 participants in 1 study | **7.54**<br>Mean | **8.38**<br>Mean<br>Difference: **MD 0.84 higher**<br>(CI 95% 0.68 lower–2.36 higher) | **Moderate**<br>Due to serious imprecision[d] | REGN-EB3 probably has little or no difference on time to viral clearance compared with mAb114. |

[a] **Imprecision: very serious.** Wide confidence intervals;
[b] **Imprecision: very serious.** Wide confidence intervals;
[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
[d] **Imprecision: serious.** Wide confidence intervals.

### 3.1.1 Mechanism of action for mAb114 and REGN-EB3

**mAb114**

mAb114 is a single monoclonal neutralizing antibody which binds to a conserved epitope within the glycoprotein subunit 1 (GP1) within the receptor binding domain (RBD) *(19)*. It was derived from memory B cells from a recovered EVD patient from the 1995 EVD outbreak in Kikwit, Democratic Republic of the Congo, approximately 11 years after infection. mAb114 exerts antiviral effects by binding and neutralizing virus particles present in circulation, thus inhibiting cell entry *(20)*.

**REGN-EB3**

REGN-EB3 is a cocktail of three antibodies: atoltivimab, odesivimab and maftivimab, selected from a pool of antibodies generated in genetically engineered mice exposed to EBOV. The three antibodies bind to non-overlapping epitopes on the Ebola glycoprotein; atoltivimab binds the GP1 head, odesivimab targets the outer glycan cap, and maftivimab targets the conserved GP2 fusion loop *(10, 20)*. REGN-EB3 exerts antiviral effects by binding and neutralizing virus particles present in circulation, thus inhibiting cell entry. Activation of effector functions through antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and antibody-dependent complement deposition are also implicated in activity of REGN-EB3.

## 3.2 Recommendation for remdesivir

**Conditional recommendation against**

We suggest against treatment with remdesivir for patients with RT-PCR confirmed EVD (*conditional recommendation against*).

**Remark**
This recommendation only applies to EVD caused by Ebola virus (EBOV; Zaire ebolavirus).

### Evidence to decision

**Benefits and harms**
In patients with EVD, the effects of remdesivir on mortality and serious adverse events remain very uncertain.

Low certainty evidence indicates that remdesivir may have little or no effect on time to viral clearance.

No subgroup effects were found for age group or CT value for remdesivir vs standard of care.

**Certainty of the evidence**
Due to the lack of a standard care arm in the PALM study, indirect comparisons via the PREVAIL II study informed the estimates of remdesivir versus standard care. Whether remdesivir reduces mortality compared with standard care for patients with EVD is very uncertain, due to extremely serious imprecision, with the possibility of both large benefit and large harm, for both the lowest and highest baseline risk estimates.

Whether remdesivir increases serious adverse events is very uncertain due to very serious imprecision with wide CIs that include substantial benefit and large harm, and due to risk of bias as a result of the unblinded design of the PALM RCT.

Remdesivir may have, in relation to standard care, little or no effect on time to viral clearance.

No subgroup effects were found for age group or CT value for remdesivir versus standard of care.

**Values and preferences**
The GDG inferred that most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on mortality and other outcomes important to patients. This is particularly so when the evidence includes a possibility of important harm, such as an increase in mortality.

**Resources and other considerations**
Remdesivir is a broad-spectrum antiviral, whereas the other three therapeutics included in this guideline are neutralizing monoclonal antibodies. Due to remdesivir's different mechanism of action, there may be a rationale to include this therapeutic in future trials of combination therapy, especially for patients at higher risk of mortality.

Given the recommendation against the use of remdesivir, efforts to ensure access to drugs should focus on those that are currently recommended.

**Acceptability and feasibility**
Remdesivir was administered intravenously as a loading dose on day 1 (200 mg in adults, and adjusted for body weight in paediatric patients), followed by a daily maintenance dose (100 mg in adults) starting on day 2 and continuing for 9 to 13 days dependent on viral load. Relative to the single dose regimens of mAb114 and REGN-EB3, remdesivir is a complex therapeutic to administer, involving infusions on multiple days and regular monitoring of viral load.

## Justification

For mortality, the most important outcome for patients, absolute benefits of remdesivir versus standard care ranged from 280 fewer to 154 more deaths per 1000 patients using the lowest baseline risk estimate, and 469 fewer to 257 more deaths per 1000 patients using the highest baseline risk estimate. Given the wide CIs include both important benefit and important harm, the panel decided on a conditional recommendation against the use of remdesivir.

It remains very uncertain whether remdesivir has any important benefits relative to standard care, or whether it causes important adverse effects. Under these circumstances, the panel inferred that most fully informed patients would decline the use of remdesivir, especially if the recommended therapeutics mAb114 or REGN-EB3 are available.

In a situation where neither mAb114 or REGN-EB3 are available, some patients may accept the higher level of risk of remdesivir in terms of direct harm (due to wide CIs and uncertainty) and serious adverse events, and opt for treatment with remdesivir.

Given that the mechanism of action of remdesivir is different to the recommended neutralizing monoclonal antibodies mAb114 and REGN-EB3 there may be a rationale in including remdesivir, or alternative therapeutics with intracellular mechanism of action, in future combination therapy trials.

## Practical information

In the PALM study, remdesivir was administered intravenously as a loading dose on day 1 (200 mg in adults, and adjusted for body weight in paediatric patients), followed by a daily maintenance dose (100 mg in adults) starting on day 2 and continuing for 9 to 13 days dependent on viral load.

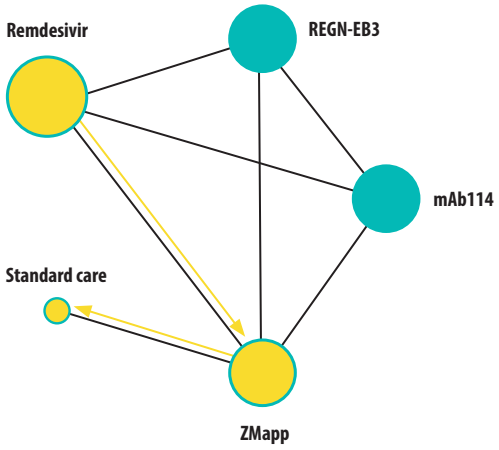
**PICO**
Population: Patients with Ebola virus disease
Intervention: Remdesivir
Comparator: Standard care

## Summary

**Evidence summary**
The evidence for remdesivir compared with standard care was informed by the PALM and PREVAIL II studies. For patients with confirmed EVD, the GRADE summary of findings table (see Fig. 4) shows the relative and absolute effects of remdesivir compared with standard care for the outcomes of interest, with certainty ratings, informed by the systematic review. The network plot of the indirect comparison between remdesivir and standard care is shown below.

The indirect comparison of remdesivir with standard care via ZMapp is shown below.

**Fig. 4 Network plot of indirect comparison of remdesivir to standard care via ZMapp**




| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Standard care | <br>Remdesivir | Certainty of the evidence<br>(Quality of evidence) | Plain language summary |
|---|---|---|---|---|---|
| Mortality<br>(absolute effect estimated from lowest baseline risk) | Relative risk: 0.64<br>(CI 95% 0.29–1.39)<br>Follow up based on indirect evidence | **395**<br>per 1000 | **253**<br>per 1000<br>Difference: **142 fewer per 1000**<br>(CI 95% 280 fewer–154 more) | **Very low**<br>Due to extremely serious imprecision[a] | Whether remdesivir reduces mortality compared with standard care is very uncertain when using the lowest baseline risk estimate. |
| Mortality<br>(absolute effect estimated from highest baseline risk) | Relative risk: 0.64<br>(CI 95% 0.29–1.39)<br>Follow up based on indirect evidence | **660**<br>per 1000 | **422**<br>per 1000<br>Difference: **238 fewer per 1000**<br>(CI 95% 469 fewer–257 more) | **Very low**<br>Due to extremely serious imprecision[b] | Whether remdesivir reduces mortality compared with standard care is very uncertain when using the highest baseline risk estimate. |
| Serious adverse events | (Risk difference: 0.022<br>(CI 95% 0.056–0.099)<br>Based on indirect evidence | Difference: **22.0 more per 1000**<br>(CI 95% 56.0 fewer–99.0 more) | | **Very low**<br>Due to serious risk of bias and very serious imprecision[c] | Whether remdesivir increases serious adverse events compared with standard care is very uncertain. |
| Time to viral clearance | Measured by days:<br>Scale: Lower better<br>Follow up based on indirect evidence | **8.68**<br>Mean | **8.41**<br>Mean<br>Difference: **MD 0.27 lower**<br>(CI 95% 3.23 lower–2.69 higher) | **Low**<br>Due to very serious imprecision[d] | Remdesivir may have little or no effect on time to viral clearance compared with standard care. |

[a] **Imprecision: extremely serious.** Wide confidence intervals;
[b] **Imprecision: extremely serious.** Wide confidence intervals;
[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **imprecision: very serious**. Wide confidence intervals;
[d] **Imprecision: very serious.** Wide confidence intervals.

### 3.2.1 Mechanism of action for remdesivir

Remdesivir is an RNA-directed RNA polymerase-inhibiting nucleoside. It exhibits broad-spectrum antiviral activity. Intracellularly, remdesivir acts as an analogue of adenosine triphosphate and directly competes with it for incorporation into nascent viral RNA, inhibiting viral replication via RNA chain termination *(21)*.

## 3.3 Recommendation for ZMapp

**Conditional recommendation against**

We suggest against treatment with ZMapp for patients with RT-PCR confirmed EVD (*conditional recommendation against*).

**Remark**
This recommendation only applies to EVD caused by Ebola virus (EBOV; Zaire ebolavirus).

### Evidence to decision

**Benefits and harms**
Although point estimates raise the possibility of an important mortality benefit and a small but potentially important increase in serious adverse events, with only 36 patients in the ZMapp and standard care groups, the evidence leaves us very uncertain regarding any true benefits or harms of ZMapp.

**Certainty of the evidence**
Whether ZMapp reduces mortality compared with standard care for patients with EVD is very uncertain, due to extremely serious imprecision, with the possibility of both large benefit and large harm, for both the lowest and highest baseline risk estimates.

Whether ZMapp increases serious adverse events is very uncertain due to very serious imprecision with wide CIs, and due to risk of bias generated by the unblinded design of the PALM RCT. ZMapp may have little or no effect on time to viral clearance compared with standard care, the low certainty evidence due to very serious imprecision, with wide CIs consistent with both important increases and important decreases in time to viral clearance. ZMapp may reduce the duration of admission compared with standard care; the low certainty evidence is due to serious risk of bias and serious imprecision.

No subgroup effects were found for mortality for ZMapp vs standard care by age group or CT value.

**Values and preferences**
The GDG inferred that most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes important to patients. This is particularly so when the possibility of important harm remains.

**Resources and other considerations**
The GDG noted that, given the recommendation against use of ZMapp, efforts to ensure access to drugs should focus on those that are currently recommended.

**Acceptability and feasibility**
Patients in the ZMapp group received an intravenous infusion of 50 mg per kg of body weight every third day beginning on day 1 (for a total of three doses). Whilst this regimen is likely to be acceptable and feasible to patients, it is more complex to administer than the single dose infusions of mAb114 and REGN-EB3.

## Justification

For mortality, the most important outcome for patients, absolute benefits of ZMapp vs standard care ranged from 284 fewer to 103 more deaths per 1000 patients using the lowest baseline risk estimate, and 475 fewer to 172 more deaths per 1000 patients using the highest baseline risk estimate. Given that the wide CIs include both important benefit and important harm, the panel decided on a conditional recommendation against the use of ZMapp.

It remains very uncertain whether ZMapp has any important benefits relative to standard care, or whether it causes important adverse effects. Under these circumstances, the panel inferred that most fully informed patients would decline the use of ZMapp, especially if the recommended therapeutics mAb114 or REGN-EB3 are available.

In a situation where neither mAb114 or REGN-EB3 are available, some patients may accept the higher level of risk of ZMapp in terms of direct harm and serious adverse events, and opt for treatment with ZMapp.

Given that the mechanism of action of ZMapp is similar to the recommended neutralizing monoclonal antibodies mAb114 and REGN-EB3, there appears to be little benefit in including ZMapp in future combination therapy trials for EVD.

## Practical information

ZMapp in the PREVAIL II RCT and PALM RCT was prescribed and administered as three intravenous infusions of 50 mg per kg of body weight, administered every third day.

**PICO**

Population: Patients with Ebola virus disease
Intervention: ZMapp
Comparator: Standard care

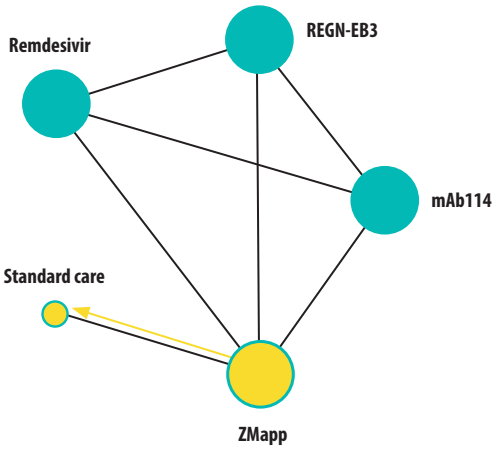
## Summary

**Evidence summary**

The evidence for ZMapp vs standard care was informed by the PREVAIL II study. PREVAIL II was an RCT of ZMapp vs standard of care. Patients were stratified according to baseline PCR CT value for the virus (≤ 22 vs > 22) and country of enrolment. Patients of any age were enrolled. No pregnant women were recruited in this trial. The primary endpoint was 28-day mortality. A total of 72 patients 36 per group were enrolled at two sites in Liberia, seven sites in Sierra Leone, one site in Guinea, and one site in the United States of America, from March to November 2015. Of the 71 patients who could be evaluated, 21 died, representing an overall CFR of 30%.

For patients with confirmed EVD, the GRADE summary of findings table (see Fig. 5) shows the relative and absolute effects of ZMapp compared with standard care for the outcomes of interest, with certainty ratings, informed by the systematic review. The network plot of the direct comparison between ZMapp and standard care is shown below.

**Fig. 5 Network plot of direct comparison between ZMapp and standard care**




| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Standard care | <br>ZMapp | Certainty of the evidence<br>(Quality of evidence) | Plain language summary |
|---|---|---|---|---|---|
| Mortality<br>(absolute effect estimated from lowest baseline risk) | Relative risk: 0.6<br>(CI 95% 0.28–1.26)<br>Based on data from 71 participants in 1 study | **395**<br>per 1000<br>Difference: **158 fewer per 1000**<br>(CI 95% 284 fewer–103 more) | **237**<br>per 1000 | **Very low**<br>Due to extremely serious imprecision[a] | Whether ZMapp reduces mortality compared with standard care is very uncertain when using the lowest baseline risk estimate. |
| Mortality<br>(absolute effect estimated from highest baseline risk) | Relative risk: 0.6<br>(CI 95% 0.28–1.26)<br>Based on data from 71 participants in 1 study | **660**<br>per 1000<br>Difference: **264 fewer per 1000**<br>(CI 95% 475 fewer–172 more) | **396**<br>per 1000 | **Very low**<br>Due to extremely serious imprecision[b] | Whether ZMapp reduces mortality compared with standard care is very uncertain when using the highest baseline risk estimate. |
| Serious adverse events | Risk difference: 0.028<br>(CI 95% 0.046–0.102)<br>Based on data from 71 participants in 1 study | Difference: **28.0 more**<br>(CI 95% 46.0 fewer–102.0 more) | | **Very low**<br>Due to serious risk of bias and very serious imprecision[c] | Whether ZMapp increases serious adverse events compared with standard care is very uncertain. |
| Time to viral clearance | Measured by days:<br>Scale: Lower better<br>Based on data from 50 participants in 1 study | **8.68**<br>Mean<br>Difference: **MD 0.25 lower**<br>(CI 95% 2.70 lower–2.20 higher) | **8.43**<br>Mean | **Low**<br>Due to very serious imprecision[d] | ZMapp may have little or no effect on time to viral clearance compared with standard care. |
| Duration of admission | Measured by days:<br>Scale: Lower better<br>Based on data from 50 participants in 1 study | **15.73**<br>Mean<br>Difference: **MD 2.02 lower**<br>(CI 95% 4.05 lower–0.01 higher) | **13.71**<br>Mean | **Low**<br>Due to serious risk of bias, and very serious imprecision[e] | ZMapp may reduce the duration of admission compared with standard care. |

[a] **Imprecision: extremely serious.** Wide confidence intervals;
[b] **Imprecision: extremely serious.** Wide confidence intervals;
[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **imprecision: very serious.** Wide confidence intervals;
[d] **Imprecision: very serious.** Wide confidence intervals;
[e] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: serious. Wide confidence intervals.

### 3.3.1 Mechanism of action for ZMapp

ZMapp is a cocktail of three monoclonal antibodies: 2G4, 4G7 and 13C6. 13C6 is a non-neutralizing humanized mouse antibody that binds to GP1 and can activate effector functions through antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and antibody-dependent complement deposition. 2G4 is a neutralizing humanized mouse antibody that binds at the GP1-GP2 interface, preventing insertion of the fusion loop into the endosome membrane. 4G7 is a neutralizing human mouse antibody that binds to the GP1-GP2 interface to prevent insertion of the fusion loop into the membrane *(19)*.

# 4. How to access and use this guideline

## How to access the guideline

- WHO website in PDF format: this is a full read out of the MAGICapp content for those without reliable web access.
- Health Care Readiness - Clinical Unit and Ebola Virus Disease: these resources were created by the Clinical Unit, Health Care Readiness, Geneva, WHO.
- The PDF can also be downloaded directly from MAGICapp (see cogwheel top right).
- MAGICapp in online, multilayered formats[5]: this is the fullest version of the guideline, as detailed below.

## How to navigate this guideline

The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

The purpose of the online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice *(22)*. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids *(23)*).

End-users will also need to understand what is meant by strong and weak/conditional recommendations (displayed immediately below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment).

For each recommendation additional information is available through the following tabs:

- **Research evidence:** Readers can find details about the research evidence underpinning the recommendations as GRADE summary of findings tables and narrative evidence summaries.
- **Evidence to decision:** The absolute benefits and harms are summarized, along with other factors such as the values and preferences of patients, practical issues around delivering the treatment as well as considerations concerning resources, applicability, feasibility, equity and human rights. These latter factors are particularly important for those adapting the guidelines for national or local contexts.
- **Justification:** Explanation of how the GDG considered and integrated evidence to decision factors when creating the recommendations, focusing on controversial and challenging issues is provided under this heading.
- **Practical information:** This section provides dosing, duration and administration of drugs, or how to apply tests to identify patients in practice.
- **Decision aids:** Here tools for shared decision-making in clinical encounters *(21)* are included.

[5] https://app.magicapp.org/#/guidelines

## Dissemination

This guideline will be disseminated via the WHO website and additional access options as detailed above. In addition a multinational EVD case management training course is planned to take place in 2022, organized by the WHO African Region, with 22 nation states invited to participate. The curriculum includes two modules on therapeutics for EVD; an efficient mechanism to disseminate this guideline.

## Additional EVD guidance and implementation tools for health workers

- *Optimized supportive care for Ebola virus disease* manual *(6)*.
- *Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease (24)*.
- Facility estimator for EVD *(25)*. This tool provides an estimation of the essential items needed to open and/or manage a treatment centre according to inputs provided by users such number of beds, average length of hospitalization and period considered.

# 5. Uncertainties and future research

Whilst the GDG were able to make strong recommendations for the use of two therapeutics, there are many remaining uncertainties. A non-exhaustive list of future research questions are listed below. There is a need for further research into EVD therapeutics, aspects of EVD supportive care, and to improve understanding and characterization of EVD as an acute and longer term disease. The GDG noted that even with the recommended therapeutics, the EVD CFR remains unacceptably high, especially for patients who present later in the disease course. The GDG noted that no data are available for several outcomes prioritized by patients and the GDG, including functional status post EVD and risk of onward transmission.

## Areas of future research

Cross-cutting research needs are to develop core outcome sets for EVD trials, increase use of standardized case report forms, and ensure continued inclusion of vulnerable populations (pregnant women, neonates, children and older people).

## Therapeutics

- What is the optimal dosage of mAb114 and REGN-EB3? Are fractionated doses of neutralizing monoclonal antibodies more efficacious? If any, what is the optimal Fc effector function/characteristics for EBOV-specific antibodies?
- What is the association (if any) between the use of neutralizing monoclonal antibodies and clinical sequelae or viral persistence in EVD survivors?
- Are there significant interactions between neutralizing monoclonal antibodies targeting the EBOV-GP and EVD vaccines incorporating EBOV-GP when administered concurrently?
- Does combination therapy with a neutralizing monoclonal antibody plus another agent reduce mortality compared with the use of single monoclonal antibody therapy?
- Is there a potential risk of viral resistance caused by selective pressure of neutralizing monoclonal antibodies?
- Is there a role for neutralizing monoclonal antibodies for post-exposure prophylaxis for high-risk exposures?
- Which novel therapeutics have the most promising breadth of pan filovirus activity? Which novel therapeutics are the most effective in terms of penetration into immune-privileged sites?

## Optimized supportive care

- Can a bundle of optimized supportive care and therapeutics reduce the CFR in the highest risk patients? What is the optimal composition of bundled care for EVD?
- How can optimized supportive care for all EVD patients be implemented, especially at the beginning of an outbreak?
- What renal replacement interventions are most effective and feasible for patients with EVD?
- What is the influence of co-existing or super infection with endemic pathogens (for example, malaria, HIV), on disease course and outcomes?

## Rapid diagnostic tests

- How can rapid diagnostic tests for EVD complement existing testing strategies?
- Can rapid diagnostic tests identify EVD patients earlier and reduce delays to treatment?

## Disease characterization

There is a need to develop our understanding of the natural history of the disease, including both acute EVD and EVD sequelae.

- What is the pathogenesis of end organ failure in EVD (e.g. mechanism of acute kidney injury)?
- What is the incidence and symptomology of EVD sequelae? What are the mechanisms underlying EVD sequelae? How can EVD sequelae be prevented and/or managed?
- What is the prevalence of viral persistence in recovered EVD patients at different timepoints after recovery? What is the incidence/frequency of relapse? What is the potential for onward transmission of EVD from a recovered patient to another person?

The GDG noted that the available RCTs concerned only EVD caused by EBOV (Zaire ebolavirus) and encouraged research and development for other ebolaviruses and marburgviruses.

# References


1. Kuhn JH, Adachi T, Adhikari NKJ, Arribas JR, Bah IE, Bausch DG et al. New filovirus disease classification and nomenclature. Nat. Rev Microbiol. 2019;17(5):261-263.
2. Jacob ST, Crozier I, Fischer WA, Hewlett A, Kraft CS, Vega M-ADL et al. Ebola virus disease. Nat Rev Dis Primers. 2020;6(1):13.
3. Kawuki J, Musa TH, Yu X. Impact of recurrent outbreaks of Ebola virus disease in Africa: a meta-analysis of case fatality rates. Public Health. 2021;195 89-97.
4. Ebola virus disease factsheet. Geneva: World Health Organization; 2021.
5. Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D et al. A randomized, controlled trial of Ebola virus disease therapeutics. New Engl J Med. 2019;381(24):2293-2303.
6. Optimized supportive care for Ebola virus disease: clinical management standard operating procedures. Geneva: World Health Organization; 2019.
7. Lamontagne F, Fowler RA, Adhikari NK, Murthy S, Brett-Major DM, Jacobs M et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. Lancet. 2018;391(10121):700-708.
8. WHO handbook for guideline development. Geneva: World Health Organization; 2014.
9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
10. Therapeutics for Ebola virus disease. Guideline Development Group meeting, 17 November 2021. Geneva: World Health Organization; 2021 (https://www.who.int/publications/m/item/meeting-report-of-the-first-gdg-meeting-for-therapeutics-for-ebola-virus-disease-%28evd%29, accessed 1 August 2022).
11. Disease Outbreak News (DONs). Geneva: World Health Organization; 2022 (https://www.who.int/emergencies/disease-outbreak-news, accessed 1 August 2022).
12. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ. 2020;192(32):E901-E906.
13. Gao Y, Zhao Y, Guyatt G, Fowler R, Kojan R, Ge L, Tian J, Hao Q. Effects of therapies for Ebola virus disease: a systematic review and network meta-analysis. Lancet Microbe. 2022 DOI: https://doi.org/10.1016/S2666-5247(22)00123-9.
14. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049-51.
15. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.
16. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
17. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
18. Davey RT, Nordwall J, Proschan MA. Trial of ZMapp for Ebola virus infection. New Engl J Med. 2017;376(7):700-701.
19. Hargreaves A, Brady C, Mellors J, Tipton T, Carroll MW, Longet S. Filovirus neutralising antibodies: mechanisms of action and therapeutic application. Pathogens. 2021;10(9):1201.
20. Tshiani Mbaya O, Mukumbayi P, Mulangu S. Review: insights on current FDA-approved monoclonal antibodies against Ebola virus infection. Front Immunol. 2021;12:721328.
21. Hoenen T, Groseth A, Feldmann H. Therapeutic strategies to target the Ebola virus life cycle. Nat Rev Microbiol. 2019;17(10):593-606.
22. Vandvik PO, Brandt L, Alonso-Coello P, Treweek S, Akl EA, Kristiansen A et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. Chest. 2013;144(2):381-389.
23. Agoritsas T, Heen AF, Brandt L, Alonso-Coello P, Kristiansen A, Akl EA et al. Decision aids that really promote shared decision making: the pace quickens. BMJ. 2015;350:g7624.
24. Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/330851, accessed 1 August 2022).
25. Essential Items Estimator Tool (Ebola); 2022 (https://essentialitemsestimator.com/, accessed 1 August 2022).

# Annex 1

## Neutralizing monoclonal antibody mAb114 for Ebola virus disease (EVD): guidance for health care workers

# Neutralizing monoclonal antibody **mAb114** for Ebola virus disease (EVD)

*mAb114 is also known by the commercial name Ebanga™ and molecular name ansuvimab.*

**Guidance for health care workers**

Both mAb114 and REGN-EB3 are recommended for use in EVD. The two drugs should not be given together. The choice of which monoclonal antibody to use depends on availability, including emerging information about effectiveness.

## CLINICAL INDICATIONS

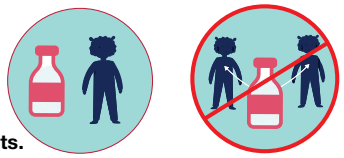
- All patients with RT-PCR confirmed EVD caused by Zaire ebolavirus, including children, pregnant women, breastfeeding women and older people.
- Neonates < 7 days, without EVD RT-PCR confirmation, born to mothers with RT-PCR confirmed EVD.

Patients should receive mAb114 as soon as possible after confirmation of RT-PCR diagnosis of EVD.

## AVAILABLE FORMULATION

A vial contains: 400 mg off-white to white lyophilized powder. Upon reconstitution, one vial contains 8 mL of solution, containing 50 mg/mL of **mAb114**.

**Note: Each vial is used for only one patient, it must not be used for multiple patients.**



## STORAGE

### Prior to reconstitution

Store refrigerated at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light. Do not freeze. Do not shake.


### Expiry

The expiration date for the product is available via a product-specific website which is frequently updated. Access the website using the QR code provided on the product.

### After reconstitution

The maximum storage time for reconstituted solution in the vial and the diluted solution in the IV bag is **4 hours**.

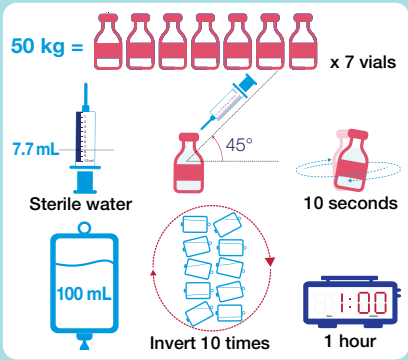
- *If the infusion is stopped for any reason*, it can be restarted on the same patient as long as the time from dilution to restarting and completing the infusion remains within 4 hours.
- *If the timeframe has been exceeded* the remaining dosage required for the patient should be calculated, new vials prepared, diluted then administered and the excess diluted drug should be safely disposed. Drugs should not be moved from high-risk to low-risk zones for temporary storage.

## DOSAGE AND ROUTE

The dose of **mAb114** for adult and paediatric patients is **50 mg/kg (or 1 mL/kg)** reconstituted with sterile water for injection, further diluted and administered as a single intravenous (IV) infusion over 60 minutes.

**EXAMPLE: Patient weighting 50 kg**

- Recommended dose is 2500 mg mAb114 OR 50 mL of mAb114.
- The dosage requires 7 vials.
- Insert in each of the vials: 7.7 mL of sterile water for injection using a sterile 10-mL syringe and an 18-gauge needle. Holding horizontally, angle the needle down at an approximate 45° angle, above the lyophilized powder. Slowly inject the diluent along the wall of the vial and without any air to avoid foaming and bubbles. Swirl them gently for 10 seconds and leave them to rest for 10 seconds until all the powder is dissolved. Repeat until the powder is dissolved. This may take up to 20 minutes
- The total of the mAb114 vials should be 50 mL and should be added to 50 mL of dilution solution (0.9% sodium chloride or Ringer's lactate) to make a total of 100 mL diluted infusion solution.
- Invert 10 times (do not shake).
- Infuse the 100 mL of diluted infusion solution over 60 minutes.



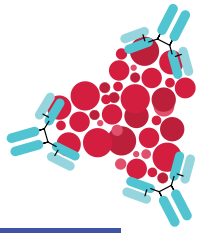

World Health Organization

Neutralizing monoclonal antibody mAb114 for Ebola virus disease (EVD)
2 August 2022



WHO reference number: WHO/EVD/therapeutics/mAb114/Poster_A/2022.1

# Preparation and administration of **mAb114** for Ebola virus disease (EVD)



**1. CALCULATE DOSE 2. RECONSTITUTE 3. DILUTE 4. ADMINISTER 5. MONITOR**

## 1. CALCULATE DOSE

- **Weigh** the patient.
- **Calculate** the dose as per Table 1.

**TABLE 1. mAb114 dose, number of vials required, volume of dilution solution to add to mAb114, final infusion solution volume**

| Body weight (kg) | Volume of mAb114 (mL) | Number of vials | Volume of dilution solution to add to reconstituted mAb114 (mL) | Total diluted infusion solution (mL) (mAb114 and dilution solution) |
|---|---|---|---|---|
| 1 | 1 | 1 | 5 | 6 |
| 2 | 2 | 1 | 10 | 12 |
| 3 | 3 | 1 | 10 | 13 |
| 4 | 4 | 1 | 10 | 14 |
| 5 | 5 | 1 | 10 | 15 |
| 6 | 6 | 1 | 10 | 16 |
| 7 | 7 | 1 | 10 | 17 |
| 8 | 8 | 1 | 10 | 18 |
| 9 | 9 | 2 | 10 | 19 |
| 10 | 10 | 2 | 10 | 20 |
| 11 | 11 | 2 | 25 | 36 |
| 12 | 12 | 2 | 25 | 37 |
| 13 | 13 | 2 | 25 | 38 |
| 14 | 14 | 2 | 25 | 39 |
| 15 | 15 | 2 | 25 | 40 |
| 16 | 16 | 2 | 25 | 41 |
| 17 | 17 | 3 | 25 | 42 |
| 18 | 18 | 3 | 25 | 43 |
| 19 | 19 | 3 | 25 | 44 |
| 20 | 20 | 3 | 25 | 45 |
| 21 | 21 | 3 | 25 | 46 |
| 22 | 22 | 3 | 25 | 47 |
| 23 | 23 | 3 | 25 | 48 |
| 24 | 24 | 3 | 25 | 49 |
| 25 | 25 | 4 | 25 | 50 |
| 26 | 26 | 4 | 50 | 76 |
| 27 | 27 | 4 | 50 | 77 |
| 28 | 28 | 4 | 50 | 78 |
| 29 | 29 | 4 | 50 | 79 |
| 30 | 30 | 4 | 50 | 80 |
| 31 | 31 | 4 | 50 | 81 |
| 32 | 32 | 4 | 50 | 82 |
| 33 | 33 | 5 | 50 | 83 |
| 34 | 34 | 5 | 50 | 84 |
| 35 | 35 | 5 | 50 | 85 |
| 36 | 36 | 5 | 50 | 86 |
| 37 | 37 | 5 | 50 | 87 |
| 38 | 38 | 5 | 50 | 88 |
| 39 | 39 | 5 | 50 | 89 |
| 40 | 40 | 5 | 50 | 90 |
| 41 | 41 | 6 | 50 | 91 |
| 42 | 42 | 6 | 50 | 92 |
| 43 | 43 | 6 | 50 | 93 |
| 44 | 44 | 6 | 50 | 94 |
| 45 | 45 | 6 | 50 | 95 |
| 46 | 46 | 6 | 50 | 96 |
| 47 | 47 | 6 | 50 | 97 |
| 48 | 48 | 6 | 50 | 98 |
| 49 | 49 | 7 | 50 | 99 |
| 50 | 50 | 7 | 50 | 100 |
| 51 | 51 | 7 | 100 | 151 |
| 52 | 52 | 7 | 100 | 152 |
| 53 | 53 | 7 | 100 | 153 |
| 54 | 54 | 7 | 100 | 154 |
| 55 | 55 | 7 | 100 | 155 |
| 56 | 56 | 7 | 100 | 156 |
| 57 | 57 | 8 | 100 | 157 |
| 58 | 58 | 8 | 100 | 158 |
| 59 | 59 | 8 | 100 | 159 |
| 60 | 60 | 8 | 100 | 160 |
| 61 | 61 | 8 | 100 | 161 |
| 62 | 62 | 8 | 100 | 162 |
| 63 | 63 | 8 | 100 | 163 |
| 64 | 64 | 8 | 100 | 164 |
| 65 | 65 | 9 | 100 | 165 |
| 66 | 66 | 9 | 100 | 166 |
| 67 | 67 | 9 | 100 | 167 |
| 68 | 68 | 9 | 100 | 168 |
| 69 | 69 | 9 | 100 | 169 |
| 70 | 70 | 9 | 100 | 170 |
| 71 | 71 | 9 | 100 | 171 |
| 72 | 72 | 9 | 100 | 172 |
| 73 | 73 | 10 | 100 | 173 |
| 74 | 74 | 10 | 100 | 174 |
| 75 | 75 | 10 | 100 | 175 |
| 76 | 76 | 10 | 100 | 176 |
| 77 | 77 | 10 | 100 | 177 |
| 78 | 78 | 10 | 100 | 178 |
| 79 | 79 | 10 | 100 | 179 |
| 80 | 80 | 10 | 100 | 180 |
| 81 | 81 | 11 | 100 | 181 |
| 82 | 82 | 11 | 100 | 182 |
| 83 | 83 | 11 | 100 | 183 |
| 84 | 84 | 11 | 100 | 184 |
| 85 | 85 | 11 | 100 | 185 |
| 86 | 86 | 11 | 100 | 186 |
| 87 | 87 | 11 | 100 | 187 |
| 88 | 88 | 11 | 100 | 188 |
| 89 | 89 | 12 | 100 | 189 |
| 90 | 90 | 12 | 100 | 190 |
| 91 | 91 | 12 | 100 | 191 |
| 92 | 92 | 12 | 100 | 192 |
| 93 | 93 | 12 | 100 | 193 |
| 94 | 94 | 12 | 100 | 194 |
| 95 | 95 | 12 | 100 | 195 |
| 96 | 96 | 12 | 100 | 196 |
| 97 | 97 | 13 | 100 | 197 |
| 98 | 98 | 13 | 100 | 198 |
| 99 | 99 | 13 | 100 | 199 |
| 100 | 100 | 13 | 100 | 200 |

World Health Organization

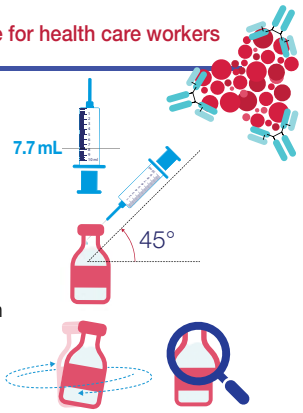
Preparation and administration of mAb114 for Ebola virus disease (EVD)
2 August 2022



WHO reference number: WHO/EVD/therapeutics/mAb114/Poster_B/2022.1

Preparation and administration of **mAb114** for Ebola virus disease (EVD) Guidance for health care workers

## 2. RECONSTITUTE

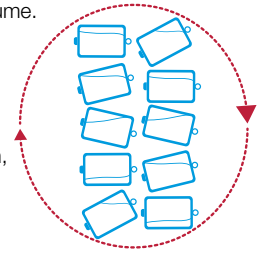



- **Prepare** mAb114 in a clean dedicated space in a low-risk zone.
- **Wash** hands per protocol.
- **Remove** mAb114 vials from refrigerator and allow them to reach room temperature.
- **Check** there is no discolouration in the content of any vial.
- **Take** 7.7 mL sterile water for injection using a sterile 10 mL syringe and an 18-gauge needle.
- **Insert** the needle tip into the mAb114 vial. Holding horizontally, angle the needle down at an approximate 45° angle, above the lyophilized powder. Slowly inject the sterile water for injection along the wall of the vial and without any air to avoid foaming and bubbles.
- **Swirl** gently (do NOT shake) for approximately 10 seconds; then set the vial down to rest for at least 10 seconds. Repeat until the powder is dissolved. This may take up to 20 minutes.
- **Check** the reconstituted solution for discolouration or visible particles; if present do NOT administer and discard the vial.

## 3. DILUTION

**Following reconstitution, mAb114 must be further diluted prior to IV infusion.**

- **Select** an appropriate amount of dilution solution, either:
  – 0.9% sodium chloride or
  – Ringer's lactate solution.
- **Withdraw and discard the quantity of** solution from the IV bag until you reach the appropriate volume of dilution solution (Table 1, column 4) with an 18–20 gauge 1–1.5" needle and an appropriately sized syringe, using standard aseptic technique.
- **Withdraw** the calculated volume of reconstituted mAb114 from the vial(s).
- **Inject** mAb114 into the dilution solution to reach total diluted infusion solution volume.
- **Invert** the IV bag 10 times to ensure thorough mixing. Do not shake.
- **Label** the IV bag with the patient's name, date of birth, weight in kg, dose of mAb114 included and date and time of drug expiration.

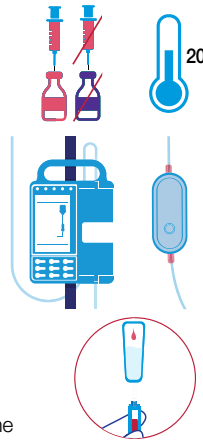


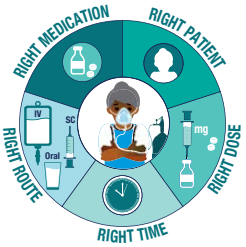
**Note:** For paediatric patients use a 10-mL syringe and infusion pump.

## 4. ADMINISTER

**Introduce** yourself to the patient and explain that you are planning to administer the medication.

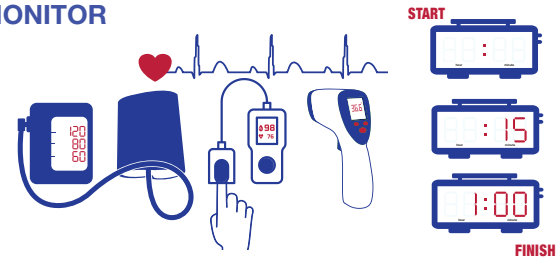
- **Do not mix** with or administer with other medicinal products.
- **Allow** the diluted infusion solution to reach room temperature prior to administration.
- **Administer** the diluted infusion solution over 60 minutes, via infusion pump (for paediatric patients < 20 kg it is preferable) or manually through an intravenous giving set containing a **sterile 1.2 micron polyether sulfone (PES) filter membrane, DEHP-free, latex-free**.
  If manually: *drip rate = (total volume (mL) / minutes) x drop factor**
  ** Check the giving set packaging!*
- **Record** the time and date the infusion was started.
- **Flush the line** at the end of the infusion.
  – If a syringe pump was used, then remove the syringe and flush the line with 2–5 mL of IV solution.
  – If an infusion bag was used, replace the empty bag and flush the line by infusing at least 25 mL of IV solution, to ensure complete product administration.




## 5. MONITOR

- Monitor patient symptoms and vital signs: heart rate, blood pressure, respiratory rate and oxygen saturation:
  – immediately before infusion
  – 15 minutes after starting the infusion
  – at the end of the infusion
  – if any clinical deterioration during the infusion, take vital signs more frequently and assess the patient clinically.




World Health Organization

Preparation and administration of mAb114 for Ebola virus disease (EVD)
2 August 2022

WHO reference number: WHO/EVD/therapeutics/mAb114/Poster_B/2022.1

## HYPERSENSITIVITY AND INFUSION REACTIONS

Hypersensitivity reactions including infusion-associated events have been reported during and post-infusion with mAb114. The most common adverse events (incidence ≥ 20%) are pyrexia, chills, tachycardia, tachypnoea and vomiting. The rate of infusion of mAb114 may be slowed or interrupted if the patient develops any signs of infusion-associated events.

IF SIGNS OR SYMPTOMS OF A CLINICALLY SIGNIFICANT HYPERSENSITIVITY REACTION OR ANAPHYLAXIS OCCUR, **IMMEDIATELY DISCONTINUE THE INFUSION** AND INITIATE APPROPRIATE MEDICATIONS, SUPPORTIVE THERAPY AND AIRWAY MANAGEMENT.

## INFUSION REACTION GUIDE

**Suggestions only – not meant to replace existing clinical guidelines or alter clinical judgment.**

| INFILTRATION | FEVER | HYPERTENSION | OTHER SYMPTOMS: | SEIZURES | ANAPHYLAXIS | ALLERGIC REACTION |
|---|---|---|---|---|---|---|
| (Watch for pain, swelling, tightness around injection site; skin cooling/ blanching; leakage at insertion site)<br>1. STOP infusion<br>2. Discontinue IV site, bandage, apply heat OR cold if available<br>3. Insert new peripheral IV | | | SHIVERING<br>HYPOTENSION<br>OEDEMA<br>PERIPHERAL NEUROPATHY | | | |
| | **38 °C – 39 °C**<br>1. Continue infusion, monitor vital signs<br>2. Administer paracetamol | **Mild**<br>1. Continue infusion, monitor vital signs | **Mild**<br>1. Continue infusion, monitor vital signs | **Brief, no loss of consciousness**<br>1. Continue infusion, monitor patient | | |
| | **39 °C – 40 °C**<br>1. Reduce infusion rate by 50%<br>2. Monitor until temperature is < 39 °C, then resume regular rate increase<br>3. Administer paracetamol per schedule | **BP > 140/90 (OR increase of diastolic pressure > 20 mmHg)**<br>1. Reduce infusion rate by 50%<br>2. Monitor BP every 15 min until BP is < 140/90, then resume regular infusion schedule | **Moderate**<br>1. Reduce infusion rate by 50%<br>2. Monitor until symptoms are reduced to mild<br>3. Resume regular infusion schedule | **Self limiting seizure**<br>1. STOP infusion.<br>2. Monitor vital signs q 15 min for 15–30 min.<br>3. If vital signs are stable and seizure does not recur, resume regular infusion schedule | **Moderate**<br>1. STOP infusion<br>2. Administer IV diphenhydramine<br>3. Notify site physician as soon as possible<br>4. Continue to administer regular IV fluid<br>5. Monitor vital signs q 15 min until reaction subsides and patient stabilizes | **Moderate**<br>1. Reduce infusion rate by 50%<br>2. Administer IV diphenhydramine<br>3. Administer IV fluids<br>4. Monitor patient q 15 minutes until symptoms are reduced to Grade 1 or below, then resume regular infusion schedule |
| | **> 40 °C**<br>1. STOP infusion<br>2. Continue to administer regular IV fluid, paracetamol<br>3. External cooling measures (if available)<br>4. When temperature is < 39 °C, resume infusion rate at 50%<br>5. Monitor at 50% rate for 15–30 min with vital signs q 15 min<br>6. If reaction does not re-occur, resume regular infusion schedule | **BP > 160/100 (OR increase of diastolic pressure > 30 mmHg)**<br>1. STOP infusion<br>2. Administer BP medications if available<br>3. When BP is reduced < 140/90, resume infusion rate at 50%<br>4. Monitor at 50% rate for 15–30 min with vital signs q 15 min<br>5.If reaction does not re-occur, resume regular infusion schedule | **Severe**<br>1. STOP infusion<br>2. When symptoms are reduced to mild, resume infusion rate at 50%<br>3. Monitor at 50% rate for 15–30 min<br>4. If reaction does not re-occur, resume regular infusion schedule | **Persistent seizures**<br>1. STOP infusion<br>2. Assess and secure airway<br>3. Continue to administer regular IV fluid, diazepam<br>4. Monitor vital signs every 15 min until seizures subside and patient stabilizes<br>5. When stable, resume infusion at 50% previous rate<br>6. Monitor for 15–30 min with vital signs every 15 min<br>7. If seizures do not re-occur, resume regular infusion schedule | **Severe**<br>1. STOP infusion<br>2. Assess and secure airway<br>3. Administer IM epinepherine<br>4. Supplemental oxygen<br>5. Volume resuscitation: 1–2 L IV as needed<br>6. For broncho-spasm resistant to IM epinephrine, give salbutamol via nebulizer, or inhaler<br>7. IV diphen-hydramine<br>8. Monitor vital signs q 15 min until reaction subsides and patient stabilizes | |

**REPORT:** Access the website using the QR code provided on the product.

World Health Organization

Preparation and administration of mAb114 for Ebola virus disease (EVD)
2 August 2022



WHO reference number: WHO/EVD/therapeutics/mAb114/Poster_B/2022.1

# Annex 2

## Neutralizing monoclonal antibody cocktail REGN-EB3 for Ebola virus disease (EVD): guidance for health care workers

# Neutralizing monoclonal antibody cocktail **REGN-EB3** for Ebola virus disease (EVD)

*REGN-EB3 is also known by the commercial name INMAZEB™ and molecular names atoltivimab, maftivimab, odesivimab.*

**Guidance for health care workers**

Both the REGN-EB3 and mAb114 are recommended for use in EVD. The two drugs should not be given together. The choice of which monoclonal antibody to use depends on availability, including emerging information about effectiveness.

## CLINICAL INDICATIONS

- All patients with RT-PCR confirmed EVD caused by Zaire ebolavirus, including children, pregnant women, breastfeeding women and older people.
- Neonates < 7 days, without EVD RT-PCR confirmation, born to mothers with RT-PCR confirmed EVD.

Patients should receive REGN-EB3 as soon as possible after confirmation of RT-PCR diagnosis of EVD.

## AVAILABLE FORMULATION

A vial of **REGN-EB3** (14.5 mL) contains:

- 241.7 mg (16.67 mg per mL) of **atoltivimab**
- 241.7 mg (16.67 mg per mL) of **maftivimab**
- 241.7 mg (16.67 mg per mL) of **odesivimab.**

**Note: Each vial is used for only one patient, it must not be used for multiple patients.**

## DOSAGE AND ROUTE

The recommended dosage of **REGN-EB3** is **150 mg/kg** (equivalent to **3 mL/kg**):

- 50 mg of **atoltivimab per kg**
- 50 mg of **maftivimab per kg**
- 50 mg of **odesivimab per kg**

diluted and administered as a single intravenous (IV) infusion.

**Volume of** REGN-EB3 needed (mL) = body weight (kg) x 3

**Number of vials** of REGN-EB3 needed = volume of REGN-EB3 / 14.5

## STORAGE



### Prior to dilution

Store REGN-EB3 vial refrigerated at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light. Do not freeze or shake.

### After dilution

The maximum duration between preparation of the diluted REGN-EB3 to completion of administration to the patient depends on the dilution solution used and the storage conditions within the times in table one.

- *If the infusion is stopped for any reason*, it can be restarted as long as the time from dilution to completing the infusion remains within the time stated in table one.
- *If the timeframe has been exceeded* the remaining dosage required for the patient should be calculated, new vials prepared, diluted then administered and the excess diluted drug should be safely disposed. Drugs should not be moved from high-risk to low-risk zones for temporary storage.

**TABLE 1. Storage conditions depending on the different dilution solutions**

| Dilution solution | Storage conditions |
|---|---|
| 0.9% sodium chloride | Store at room temperature up to 25 °C for no more than **8 hours** or refrigerated at 2 °C to 8 °C for no more than **24 hours**. |
| 5% dextrose solution or Ringer's lactate solution | Store at room temperature up to 25 °C for no more than **4 hours** or refrigerated at 2 °C to 8 °C for no more than **4 hours**. |

### Expiry

The expiration date for the product is available via a product-specific website, which is frequently updated (www.regeneron.com).

World Health Organization

Neutralizing monoclonal antibody cocktail REGN-EB3 for Ebola virus disease (EVD)
2 August 2022



WHO reference number: WHO/EVD/therapeutics/REGN-EB3/Poster_A/2022.1

# Preparation and administration of **REGN-EB3** for Ebola virus disease (EVD)

**1. CALCULATE DOSE 2. DILUTE 3. ADMINISTER 4. MONITOR**

## 1. CALCULATE DOSE

- Weigh the patient.
- Calculate the dose as per Table 2.

**TABLE 2. Dose, number of vials, total diluted infusion volume and infusion time of REGN-EB3**

| Body weight (kg) | Dose of REGN-EB3 (mg) | Volume of dose REGN-EB3 (mL) | Number of vials | Total diluted infusion solution (REGN-EB3 and dilution solution) (mL) | Infusion time of diluted infusion solution |
|---|---|---|---|---|---|
| 1 | 50 | 3 | 1 | 15 | 4 hours |
| 2 | 100 | 6 | 1 | 25 | 4 hours |
| 3 | 150 | 9 | 1 | 25 | 3 hours |
| 4 | 200 | 12 | 1 | 50 | 3 hours |
| 5 | 250 | 15 | 2 | 50 | 3 hours |
| 6 | 300 | 18 | 2 | 50 | 3 hours |
| 7 | 350 | 21 | 2 | 50 | 3 hours |
| 8 | 400 | 24 | 2 | 100 | 3 hours |
| 9 | 450 | 27 | 2 | 100 | 3 hours |
| 10 | 500 | 30 | 3 | 100 | 3 hours |
| 11 | 550 | 33 | 3 | 100 | 3 hours |
| 12 | 600 | 36 | 3 | 100 | 3 hours |
| 13 | 650 | 39 | 3 | 100 | 3 hours |
| 14 | 700 | 42 | 3 | 100 | 3 hours |
| 15 | 750 | 45 | 4 | 100 | 3 hours |
| 16 | 800 | 48 | 4 | 250 | 2 hours |
| 17 | 850 | 51 | 4 | 250 | 2 hours |
| 18 | 900 | 54 | 4 | 250 | 2 hours |
| 19 | 950 | 57 | 4 | 250 | 2 hours |
| 20 | 1000 | 60 | 5 | 250 | 2 hours |
| 21 | 1050 | 63 | 5 | 250 | 2 hours |
| 22 | 1100 | 66 | 5 | 250 | 2 hours |
| 23 | 1150 | 69 | 5 | 250 | 2 hours |
| 24 | 1200 | 72 | 5 | 250 | 2 hours |
| 25 | 1250 | 75 | 6 | 250 | 2 hours |
| 26 | 1300 | 78 | 6 | 250 | 2 hours |
| 27 | 1350 | 81 | 6 | 250 | 2 hours |
| 28 | 1400 | 84 | 6 | 250 | 2 hours |
| 29 | 1450 | 87 | 6 | 250 | 2 hours |
| 30 | 1500 | 90 | 7 | 250 | 2 hours |
| 31 | 1550 | 93 | 7 | 250 | 2 hours |
| 32 | 1600 | 96 | 7 | 250 | 2 hours |
| 33 | 1650 | 99 | 7 | 250 | 2 hours |
| 34 | 1700 | 102 | 8 | 250 | 2 hours |
| 35 | 1750 | 105 | 8 | 250 | 2 hours |
| 36 | 1800 | 108 | 8 | 250 | 2 hours |
| 37 | 1850 | 111 | 8 | 250 | 2 hours |
| 38 | 1900 | 114 | 8 | 250 | 2 hours |
| 39 | 1950 | 117 | 9 | 500 | 2 hours |
| 40 | 2000 | 120 | 9 | 500 | 2 hours |
| 41 | 2050 | 123 | 9 | 500 | 2 hours |
| 42 | 2100 | 126 | 9 | 500 | 2 hours |
| 43 | 2150 | 129 | 9 | 500 | 2 hours |
| 44 | 2200 | 132 | 10 | 500 | 2 hours |
| 45 | 2250 | 135 | 10 | 500 | 2 hours |
| 46 | 2300 | 138 | 10 | 500 | 2 hours |
| 47 | 2350 | 141 | 10 | 500 | 2 hours |
| 48 | 2400 | 144 | 10 | 500 | 2 hours |
| 49 | 2450 | 147 | 11 | 500 | 2 hours |
| 50 | 2500 | 150 | 11 | 500 | 2 hours |
| 51 | 2550 | 153 | 11 | 500 | 2 hours |
| 52 | 2600 | 156 | 11 | 500 | 2 hours |
| 53 | 2650 | 159 | 11 | 500 | 2 hours |
| 54 | 2700 | 162 | 12 | 500 | 2 hours |
| 55 | 2750 | 165 | 12 | 500 | 2 hours |
| 56 | 2800 | 168 | 12 | 500 | 2 hours |
| 57 | 2850 | 171 | 12 | 500 | 2 hours |
| 58 | 2900 | 174 | 12 | 500 | 2 hours |
| 59 | 2950 | 177 | 13 | 500 | 2 hours |
| 60 | 3000 | 180 | 13 | 500 | 2 hours |
| 61 | 3050 | 183 | 13 | 500 | 2 hours |
| 62 | 3100 | 186 | 13 | 500 | 2 hours |
| 63 | 3150 | 189 | 14 | 500 | 2 hours |
| 64 | 3200 | 192 | 14 | 500 | 2 hours |
| 65 | 3250 | 195 | 14 | 500 | 2 hours |
| 66 | 3300 | 198 | 14 | 500 | 2 hours |
| 67 | 3350 | 201 | 14 | 500 | 2 hours |
| 68 | 3400 | 204 | 15 | 500 | 2 hours |
| 69 | 3450 | 207 | 15 | 500 | 2 hours |
| 70 | 3500 | 210 | 15 | 500 | 2 hours |
| 71 | 3550 | 213 | 15 | 500 | 2 hours |
| 72 | 3600 | 216 | 15 | 500 | 2 hours |
| 73 | 3650 | 219 | 16 | 500 | 2 hours |
| 74 | 3700 | 222 | 16 | 500 | 2 hours |
| 75 | 3750 | 225 | 16 | 500 | 2 hours |
| 76 | 3800 | 228 | 16 | 500 | 2 hours |
| 77 | 3850 | 231 | 16 | 500 | 2 hours |
| 78 | 3900 | 234 | 17 | 500 | 2 hours |
| 79 | 3950 | 237 | 17 | 500 | 2 hours |
| 80 | 4000 | 240 | 17 | 1000 | 2 hours |
| 81 | 4050 | 243 | 17 | 1000 | 2 hours |
| 82 | 4100 | 246 | 17 | 1000 | 2 hours |
| 83 | 4150 | 249 | 18 | 1000 | 2 hours |
| 84 | 4200 | 252 | 18 | 1000 | 2 hours |
| 85 | 4250 | 255 | 18 | 1000 | 2 hours |
| 86 | 4300 | 258 | 18 | 1000 | 2 hours |
| 87 | 4350 | 261 | 18 | 1000 | 2 hours |
| 88 | 4400 | 264 | 19 | 1000 | 2 hours |
| 89 | 4450 | 267 | 19 | 1000 | 2 hours |
| 90 | 4500 | 270 | 19 | 1000 | 2 hours |
| 91 | 4550 | 273 | 19 | 1000 | 2 hours |
| 92 | 4600 | 276 | 20 | 1000 | 2 hours |
| 93 | 4650 | 279 | 20 | 1000 | 2 hours |
| 94 | 4700 | 282 | 20 | 1000 | 2 hours |
| 95 | 4750 | 285 | 20 | 1000 | 2 hours |
| 96 | 4800 | 288 | 20 | 1000 | 2 hours |
| 97 | 4850 | 291 | 21 | 1000 | 2 hours |
| 98 | 4900 | 294 | 21 | 1000 | 2 hours |
| 99 | 4950 | 297 | 21 | 1000 | 2 hours |
| 100 | 5000 | 300 | 21 | 1000 | 2 hours |

**Note:** The recommended infusion volume ensures the final concentration of the diluted solution is between 9.5 mg/mL to 23.7 mg/mL

World Health Organization

Preparation and administration of REGN-EB3 for Ebola virus disease (EVD)
2 August 2022


WHO reference number: WHO/EVD/therapeutics/ REGN-EB3/Poster_B/2022.1

## 2. DILUTION

- **Prepare** REGN-EB3 in a clean dedicated space in the low-risk zone.
- **Wash** hands per protocol.
- **Remove** vials from the refrigerator and allow them to reach room temperature.
- **Check** there is no discolouration in the content of any vial.
- **Select** type of dilution solution and volume required (Table 2), either:
  – 0.9% sodium chloride
  – 5% dextrose (recommended solution for neonates) or
  – Ringer's lactate solution.
- **Withdraw and discard** solution from the IV bag equal to the calculated volume of REGN-EB3 in mL required, using appropriately sized syringe and 21-gauge needle following standard aseptic techniques.
- **Add** the calculated volume of REGN-EB3 required to the IV bag of dilution solution.
- **Invert** the IV bag 10 times to ensure thorough mixing. Do not shake.
- **Label** the IV bag with the patient's name, date of birth, weight in kg, dose of REGN-EB3 included and date/time of drug expiration.

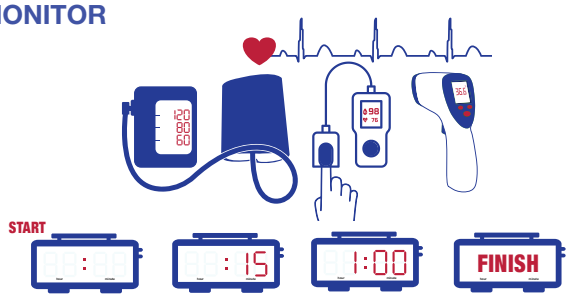
## 3. ADMINISTER

- **Introduce** yourself to the patient and explain that you are planning to administer the medication.
- **Do not mix** with or administer with other medicinal products.
- **Allow** the diluted infusion solution to reach room temperature prior to administration.
- **Administer** the diluted infusion solution via infusion pump (for paediatric patients < 20 kg it is preferable) or manually through an IV giving set containing a sterile **in-line or add-on 0.2-micron filter**.
- **Select** the appropriate infusion rate.
  If manually: *drip rate = (total volume (mL) / minutes) x drop factor**
  * *Check the giving set packaging!*
- **Record** the time and date the infusion was started.
- **Flush the line** at the end of the infusion.
  – When the infusion bag is almost empty, hang a 250-mL 0.9% sodium chloride flush bag or inject at least an additional 50 mL of 0.9% of sodium chloride into the IV infusion bag.

**Remember the FIVE RIGHTS of drug administration:**


## 4. MONITOR

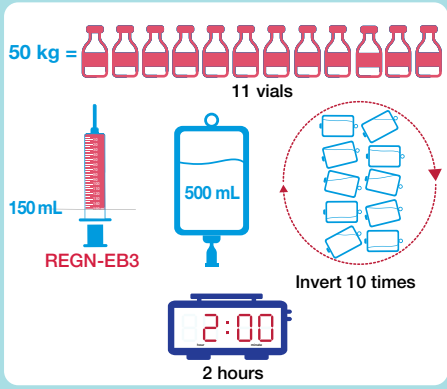
- Monitor patient symptoms and vital signs: heart rate, blood pressure, respiratory rate and oxygen saturation:
  – immediately before infusion
  – 15 minutes after starting the infusion
  – 1 hour into the infusion
  – at the end of the infusion
  – if any clinical deterioration during the infusion, take vital signs more frequently and assess the patient clinically.




**EXAMPLE**

**Patient weighting 50 kg**

- Recommended dosage is 2500 mg of atoltivimab, 2500 mg of maftivimab and 2500 mg of odesivimab OR 150 mL of REGN-EB3.
- The dosage requires 11 vials of REGN-EB3.
- Take an IV bag of 500 mL of dilution solution (0.9% sodium chloride, Ringer's lactate or 5% dextrose solution).
- Withdraw and discard 150 mL of the solution with an appropriately sized syringe and 21-gauge needle following standard aseptic techniques.
- Inject 150 mL of REGN-EB3 into the infusion solution to have a total infusion solution of 500 mL
- Invert 10 times (do not shake).
- Infuse the 500 mL of diluted infusion solution over 2 hours.

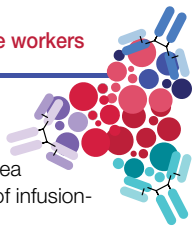



World Health Organization

Preparation and administration of REGN-EB3 for Ebola virus disease (EVD)
2 August 2022

WHO reference number: WHO/EVD/therapeutics/ REGN-EB3/Poster_B/2022.1

Preparation and administration of **REGN-EB3** for Ebola virus disease (EVD) **Guidance for health care workers**



## HYPERSENSITIVITY AND INFUSION REACTIONS

Hypersensitivity reactions including infusion-associated events have been reported during and post-infusion with REGN-EB3. The most common adverse events (incidence ≥ 20%) are pyrexia, chills, tachycardia, tachypnoea and vomiting. The rate of infusion of REGN-EB3 may be slowed or interrupted if the patient develops any signs of infusion-associated events.

IF SIGNS OR SYMPTOMS OF A CLINICALLY SIGNIFICANT HYPERSENSITIVITY REACTION OR ANAPHYLAXIS OCCUR, **IMMEDIATELY DISCONTINUE THE INFUSION** AND INITIATE APPROPRIATE MEDICATIONS, SUPPORTIVE THERAPY AND AIRWAY MANAGEMENT.

## INFUSION REACTION GUIDE

**Suggestions only – not meant to replace existing clinical guidelines or alter clinical judgment.**

| INFILTRATION | FEVER | HYPERTENSION | OTHER SYMPTOMS: | SEIZURES | ANAPHYLAXIS | ALLERGIC REACTION |
|---|---|---|---|---|---|---|
| (Watch for pain, swelling, tightness around injection site; skin cooling/ blanching; leakage at insertion site)<br>1. STOP infusion<br>2. Discontinue IV site, bandage, apply heat OR cold if available<br>3. Insert new peripheral IV | | | SHIVERING<br>HYPOTENSION<br>OEDEMA<br>PERIPHERAL NEUROPATHY | | | |
| | **38 °C – 39 °C**<br>1. Continue infusion, monitor vital signs<br>2. Administer paracetamol | **Mild**<br>1. Continue infusion, monitor vital signs | **Mild**<br>1. Continue infusion, monitor vital signs | **Brief, no loss of consciousness**<br>1. Continue infusion, monitor patient | | |
| | **39 °C – 40 °C**<br>1. Reduce infusion rate by 50%<br>2. Monitor until temperature is < 39 °C, then resume regular rate increase<br>3. Administer paracetamol per schedule | **BP > 140/90 (OR increase of diastolic pressure > 20 mmHg)**<br>1. Reduce infusion rate by 50%<br>2. Monitor BP every 15 min until BP is < 140/90, then resume regular infusion schedule | **Moderate**<br>1. Reduce infusion rate by 50%<br>2. Monitor until symptoms are reduced to mild<br>3. Resume regular infusion schedule | **Self limiting seizure**<br>1. STOP infusion.<br>2. Monitor vital signs q 15 min for 15–30 min.<br>3. If vital signs are stable and seizure does not recur, resume regular infusion schedule | **Moderate**<br>1. STOP infusion<br>2. Administer IV diphenhydramine<br>3. Notify site physician as soon as possible<br>4. Continue to administer regular IV fluid<br>5. Monitor vital signs q 15 min until reaction subsides and patient stabilizes | **Moderate**<br>1. Reduce infusion rate by 50%<br>2. Administer IV diphenhydramine<br>3. Administer IV fluids<br>4. Monitor patient q 15 minutes until symptoms are reduced to Grade 1 or below, then resume regular infusion schedule |
| | **> 40 °C**<br>1. STOP infusion<br>2. Continue to administer regular IV fluid, paracetamol<br>3. External cooling measures (if available)<br>4. When temperature is < 39 °C, resume infusion rate at 50%<br>5. Monitor at 50% rate for 15–30 min with vital signs q 15 min<br>6. If reaction does not re-occur, resume regular infusion schedule | **BP > 160/100 (OR increase of diastolic pressure > 30 mmHg)**<br>1. STOP infusion<br>2. Administer BP medications if available<br>3. When BP is reduced < 140/90, resume infusion rate at 50%<br>4. Monitor at 50% rate for 15–30 min with vital signs q 15 min<br>5.If reaction does not re-occur, resume regular infusion schedule | **Severe**<br>1. STOP infusion<br>2. When symptoms are reduced to mild, resume infusion rate at 50%<br>3. Monitor at 50% rate for 15–30 min<br>4. If reaction does not re-occur, resume regular infusion schedule | **Persistent seizures**<br>1. STOP infusion<br>2. Assess and secure airway<br>3. Continue to administer regular IV fluid, diazepam<br>4. Monitor vital signs every 15 min until seizures subside and patient stabilizes<br>5. When stable, resume infusion at 50% previous rate<br>6. Monitor for 15–30 min with vital signs every 15 min<br>7. If seizures do not re-occur, resume regular infusion schedule | **Severe**<br>1. STOP infusion<br>2. Assess and secure airway<br>3. Administer IM epinepherine<br>4. Supplemental oxygen<br>5. Volume resuscitation: 1–2 L IV as needed<br>6. For broncho-spasm resistant to IM epinephrine, give salbutamol via nebulizer, or inhaler<br>7. IV diphen-hydramine<br>8. Monitor vital signs q 15 min until reaction subsides and patient stabilizes | |

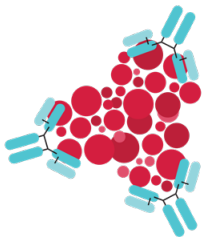
**REPORT:** Access the website using the QR code provided on the product.

World Health Organization

Preparation and administration of REGN-EB3 for Ebola virus disease (EVD)
2 August 2022



WHO reference number: WHO/EVD/therapeutics/ REGN-EB3/Poster_B/2022.1



**For further information, contact:**
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland
www.who.int

9789240055742