Application for Inclusion of Anti Ebola Virus Disease Monoclonal Antibodies to the World Health Organization's Model Lists of Essential Medicines and Essential Medicines for Children

1) Summary statement of the proposal for inclusion

This application proposes the addition of two monoclonal antibody therapeutics, ansuvimab-zykl (mAb114) and atoltivimab, maftivimab , odesivimab (REGN-EB3) for the treatment of acute Ebola virus disease, to the Essential Medicines Lists (EML) and the Essential Medicines List for Children (EMLc) for treatment of EVD for all populations with EVD.

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 application 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 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, outbreaks in the Democratic Republic of the Congo (2018–20, 2020, 2021, 2022), in Guinea (2021).[4]

International Non-proprietary Name	ansuvimab-zykl	atoltivimab, maftivimab, and odesivimab-ebgn
Name used in randomized controlled trials	mAb114	REGN-EB3

Table one: EBOV therapeutics nomenclature

Historically, there was no proven therapeutic for EVD. Until a randomized controlled trial (RCT) of antibody cocktail containing 2G4, 4G7, 13C6 (ZMapp) vs three other EBOV-specific therapeutics, was conducted in the Democratic Republic of the Congo in 2018 to 2019.[5]

In 2022, WHO published a new guideline, "Therapeutics for Ebola Virus Disease" which summarized high quality evidence for EVD therapeutics and made recommendations for their use.[6] The new WHO guideline made a strong recommendation for treatment with either (mAb114) ansuvimab-zykl or (REGN-EB3) atoltivimab, maftivimab, and odesivimab-ebgn 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*).

- (mAb114) ansuvimab-zykl and (REGN-EB3) atoltivimab, maftivimab, and odesivimab-ebgn should not be given together, and should be viewed as alternatives.

The choice of whether to use (mAb114) ansuvimab-zykl and (REGN-EB3) atoltivimab, maftivimab, and odesivimab-ebgn depends on availability.
- This recommendation only applies to EVD caused by Ebola virus (EBOV; Zaire ebolavirus).

Due to very similar evidence profiles of (mAb114) ansuvimab-zykl and (REGN-EB3) atoltivimab, maftivimab, and odesivimab-ebgn 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) ansuvimab-zykl and (REGN-EB3) atoltivimab, maftivimab, and odesivimab-ebgn versus likely have important reductions in 28 day mortality, the most important outcome for patients, relative to standard of care:

- The absolute benefit of (mAb114) ansuvimab-zykl for mortality of between 229 and 383 fewer deaths per 1000 patients is an important reduction in mortality.
- The absolute benefit of (REGN-EB3) atoltivimab, maftivimab, and odesivimab-ebgn versus for mortality of between 237 and 396 fewer deaths per 1000 patients is an important reduction in mortality.

The GDG decided extend the recommendation to neonates less than 7 days old, of unconfirmed EVD status, born to mothers with EVD in this recommendation, maintaining the eligibility criteria that was used in the 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.

This application proposes the addition of two monoclonal antibody therapeutics, (mAb114) ansuvimab-zykl and atoltivimab, maftivimab, and odesivimab-ebgn (REGN-EB3), to the EML and the Essential Medicines List for Children (EMLc) for treatment of EVD for all populations with EVD.

2) Relevant WHO technical department and focal point

Janet Diaz, Clinical Management Unit, Health care readiness, HQ.

3) Name of organization(s) consulted and/or supporting the application

Beyond the support of the WHO Guideline Development Group for Therapeutics for Ebola virus disease, no other organizations have been consulted in relation to this application.

4) International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

- INN: ansuvimab-zykl
  - Pharmacological class: *Zaire ebolavirus* glycoprotein (EBOV GP)-directed human monoclonal antibody.
- INN: cocktail atoltivimab, maftivimab, and odesivimab-ebgn
  - Pharmacological class *Zaire ebolavirus* directed human monoclonal antibody.

5) Dose

a. ansuvimab-zykl (mAb114): 50mg/kg single intravenous dose.

b. atoltivimab, maftivimab, and odesivimab-ebgn (REGN-EB3): **150 mg/kg** (equivalent to **3 mL/kg**): 50 mg of **atoltivimab**; 50 mg of **maftivimab**; and 50 mg of **odesivimab per kg** as a single intravenous dose.

6) Whether listing is requested as an individual medicine or as representative of a pharmacological Class

This application proposes the addition of two monoclonal antibody therapeutics, ansuvimab-zykl and atoltivimab, maftivimab , odesivimab, for the treatment of acute EVD, to the Essential Medicines Lists (EML) and the Essential Medicines List for Children (EMLc) for treatment of EVD for all populations with EVD.

7) Treatment details (including requirements for diagnosis, treatment and monitoring)

To maximize likelihood of therapeutic effect, (mAb114) ansuvimab-zykl or (REGN-EB3) atoltivimab, maftivimab , odesivimab should be administered as soon as possible after diagnosis of EVD by EBOV RT-PCR. Both (mAb114) ansuvimab-zykl and (REGN-EB3) atoltivimab, maftivimab , odesivimab are given as a single dose by intravenous infusion.

Ansuvimab-zykl (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, paediatric and neonatal 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.

Atoltivimab, maftivimab , odesivimab (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** and;
- 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/kg of **atoltivimab** and;
- 50 mg/kg of **maftivimab** and;
- 50 mg/kg of **odesivimab**.

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

Mechanism of action for (mAb114) ansuvimab-zykl and (REGN-EB3) atoltivimab, maftivimab , odesivimab

Ansuvimab-zykl (mAb114)

Ansuvimab-zykl (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).[7] 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. Ansuvimab-zykl (mAb114) exerts antiviral effects by binding and neutralizing virus particles present in circulation, thus inhibiting cell entry.[8]

Atoltivimab, maftivimab , odesivimab (REGN-EB3)

Atoltivimab, maftivimab, odesivimab **(**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.[8] Atoltivimab, maftivimab (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 Atoltivimab, maftivimab (REGN-EB3).

8) Review of benefits: summary of evidence of comparative effectiveness

In 2018-2019 a multicentre randomized controlled study was undertaken in Democratic Republic of Congo.[5] All patients received standard care, which consisted of administration of intravenous fluids, daily clinical laboratory testing, correction of hypoglycaemia and electrolyte imbalances, and administration of broad-spectrum antibiotic agents and antimalarial agents as indicated. Patients were assigned in a 1:1:1:1 ratio to receive 2G4, 4G7, 13C6 (ZMapp), remdesivir, Ansuvimab-zykl (*mAb114)*, or Atoltivimab, maftivimab , odesivimab (REGN-EB3). Patients of any age, including pregnant women, were eligible if they had a blood specimen positive for EBOV by real time PCR (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 Cycle Threshold (CT)values for the virus (≤ 22 vs > 22), with lower CT values corresponding to higher viral load. The primary end point was 28-day mortality. A total of 681 patients were enrolled, from 20 November 2018 to 9 August 2019. The difference in 28-day mortality of ansuvimab-zykl (*mAb114)* compared to 2G4, 4G7, 13C6 (ZMapp) was −14.6% (95%CI: −25.2 to −1.7). The difference in 28 day mortality of atoltivimab, maftivimab , odesivimab (REGN-EB3) compared to 2G4, 4G7, 13C6 (ZMapp) was −17.8% (95%CI: −28.9 to −2.9).

Both ansuvimab-zykl (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 Ansuvimab-zykl (mAb114*)* for mortality of between 229 and 383 fewer deaths per 1000 patients is an important reduction in mortality.
- The absolute benefit of Atoltivimab, maftivimab , odesivimab (REGN-EB3)for mortality of between 237 and 396 fewer deaths per 1000 patients is an important reduction in mortality.

See detailed comparative effectiveness of the two therapeutics in the table two below:

Outcome Timeframe	Study results and measurements	Absolute effect estimates mAb114	 REGN-EB3	Certainty of the evidence (Quality of evidence)	Plain language summary
Mortality (absolute effect estimated from lowest baseline risk)	Relative risk: 0.96 (CI 95% 0.71–1.29) Based on data from 329 participants in 1 study	**166** per 1000	**159** per 1000 Difference: **7 fewer per 1000** (CI 95% 48 fewer–48 more)	**Low** 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 (absolute effect estimated from highest baseline risk)	Relative risk: 0.96 (CI 95% 0.71–1.29) Based on data from 329 participants in 1 study	**277** per 1000	**266** per 1000 Difference: **11 fewer per 1000** (CI 95% 80 fewer–80 more)	**Low** 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 (CI 95% 0.012–0.012) Based on data from 329 participants in 1 study	Difference: **0.0 fewer per 1000** (CI 95% 12.0 fewer–12.0 more)		**Moderate** 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: Scale: Lower better Based on data from 216 participants in 1 study	**7.54** Mean	**8.38** Mean Difference: **MD 0.84 higher** (CI 95% 0.68 lower–2.36 higher)	**Moderate** 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.

Table two: Head to head comparison of atoltivimab, maftivimab , odesivimab (REGN-EB3) and ansuvimab-zykl (mAb114*). *Mortality refers to 28 day mortality.*

9) Review of harms and toxicity: summary of evidence of safety

Table three summarizes the adverse events that were reported in the PALM trial from a pre-defined list of signs and symptoms that occurred during Atoltivimab, maftivimab, odesivimab (REGN-EB3) and ansuvimab-zykl (mAb114) infusion. The evaluation of adverse events in subjects may have been confounded by the signs and symptoms of the underlying *Zaire ebolavirus* infection.

Twenty nine percent (n=51) of subjects who received ansuvimab-zykl (mAb114) and 20% who received atoltivimab, maftivimab , odesivimab (REGN-EB3) in the PALM Trial experienced a pre-specified infusion-related adverse event. The most common pre-specified infusion-related adverse event reported in at least 10% of subjects who received the therapeutics was fever (*Table three*). The adverse event profile in adult and pediatric subjects treated with ansuvimab-zykl (mAb114) or atoltivimab, maftivimab , odesivimab (REGN-EB3) was similar.

Adverse events	**Atoltivimab, maftivimab , odesivimab (REGN-EB3)** **(n=154)** **%**	**Ansuvimab-zykl (mAb114)** **(n=173)** **%**	**Control** **(n=168)** **%**
Pyrexia	54	17	58
Tachycardia	39	9	32
Diarrhoea	20	9	18
Vomiting	19	8	23
Hypotension	19	8	31
Tachypnoea	15	6	28
Chills	11	5	33
Hypoxia,	10	3	11

Table three: Adverse Events That Occurred During Infusion in >10% of Adult and Paediatric Subjects in the PALM Trial

10) Summary of available data on comparative cost and cost-effectiveness of the medicine

As of 1st October 2022, there is no commercial product available. The therapeutics in stock are clinical lots IND labelled and provided by Regeneron™ and Ridgeback Pharmaceuticals™. The two therapeutics are currently used under an expanded access /compassionate use protocol. The price of the two medicines are currently unknown. WHO Procurement has issued a Request for Quotations and invited the two manufacturers to make offers. No cost-effectiveness studies have been undertaken.

11) Summary of regulatory status and market availability

The two therapeutics have been approved by the United States Food and Drug Administration, (FDA).[9] In 2021 due to the evidence of efficacy of the two therapeutics WHO opened an Expression of Interest to manufacturers of the therapeutics for product evaluation and prequalification.[10]

Market availability: the International Coordinating Group (ICG) agreed in October 2021 to build a stockpile of the two therapeutics with 5000 treatments. However, there are no commercial batches available. The US government (BARDA) has an agreement with Regeneron to procure REGN-EB3 for the US National Strategic Stockpile. WHO has issued a request for quotation in 2022. Ridgeback responded that the company does not have the capacity to produce. mAb114 has been developed under an agreement with NIH. Ridgeback is in the process or agreeing a commercial partner to produce the mAbs, estimated to be in the market in 2024/2025. Regeneron has not yet submitted an offer, consequently the price remains unknown.

12) Availability of Pharmacopoeia standards

Currently, the two therapeutics are not listed in the British, European, U.S. or International Pharmacopeia.

13) References

1. Kuhn JH, Adachi T, Adhikari NKJ, et al. New filovirus disease classification and nomenclature. *Nat Rev Microbiol* 2019; **17**(5): 261-3.
2. Jacob ST, Crozier I, Fischer WA, 2nd, 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. World Health Organisation. Ebola virus disease factsheet. 2022. https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease (accessed 08/12/2022 2022).
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