

## **Notes for the record: Consultation on Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) for Ebola Virus Disease (EVD)**

A group of independent scientific experts were convened by the WHO for the purpose of updating the May 2018 statement on MEURI for Ebola virus disease (EVD) during the current outbreak, 27 August 2018.

Experts:

Dr. Edward Cox (Chair), Dr. Annick Antierens, Dr. Daniel Bausch, Dr. Sina Bavari, Dr. Marco Cavaleri, Dr. Rick Davey, Dr. Robert Fowler, Prof. Stephan Guenther, Prof. Jean-Jacques Muyembe, *Dr Gail Carson\**, *Prof. Sabue Mulangu\**, *Prof. Steve Ahuka Mundeke\**, *Prof. Stuart Nichol\**, *Dr. Tim O’Dempsey\**, *Prof. Ross Upshur\** (*\*Unable to attend but reviewed the statement prior to its finalization*).

There are many pathogens for which no proven effective intervention exists. For some pathogens there may be interventions that have shown promising safety and efficacy in the laboratory and in relevant animal models but that have not yet been evaluated for safety and efficacy in humans. Under normal circumstances, such interventions undergo testing in clinical trials that are capable of generating reliable evidence about safety and efficacy. However, in the context of an outbreak characterized by high mortality, it can be ethically appropriate to offer individual patients investigational interventions on an emergency basis outside clinical trials. The WHO developed an ethical framework known as Monitored Emergency Use of Unregistered Interventions (MEURI<sup>1</sup>) which established the following criteria to be met for access to investigational therapeutics for individual patients outside of clinical trials:

- 1) no proven effective treatment exists;
- 2) it is not possible to initiate clinical studies immediately;
- 3) data providing preliminary support of the intervention’s efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk–benefit analysis;
- 4) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use;
- 5) adequate resources are available to ensure that risks can be minimized;
- 6) the patient’s informed consent is obtained; and
- 7) the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community.

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<sup>1</sup> <http://www.who.int/ethics/publications/infectious-disease-outbreaks/en/> Chapter 9 MEURI

Against this background, and in the context of the current Ebola Zaire outbreak in eastern Democratic Republic of Congo (DRC) with a high case fatality rate, WHO convened a meeting of scientific experts to evaluate and update the available information and data on investigational therapeutics intended to treat Ebola virus disease (EVD). The purpose of the meeting was to consider whether the available information supported MEURI for access to investigational therapeutics on an individual patient basis for treatment of EVD during the current outbreak, outside of a clinical trial. (N.B., There are parallel efforts underway to establish clinical trials as soon as possible). The Committee members were provided with new information that has become available subsequent to the May 2018 consultation.

Protocol development efforts are well underway with the goal of rapidly establishing randomized controlled trials to evaluate the role of investigational agents in treating patients with EVD. The expert panel stated that while it is appropriate to provide investigational agents under MEURI, efforts should be made to create the least interference possible with the initiation, conduct, or completion of randomized controlled clinical trials that will allow for the evaluation of investigational therapeutics for treatment of patients with EVD.

Conducting randomized controlled trials will provide the best means to evaluate investigational therapies and identify the therapies that can benefit patients with EVD.

A concise summary of key points from the expert panel's deliberations updated with new information available subsequent to the May 2018 consultation include the points listed below. The panel noted that the available evidence for these investigational therapies was, in general, well below the usual level evidence for formulating recommendations. Panel members were free to express their viewpoints and contrary views were listened to respectfully.

- ZMapp (a monoclonal antibody cocktail) - The available data, including the data from a randomized controlled trial of ZMapp in patients with EVD, provide the highest quality data for the use of ZMapp under MEURI, where the panel assessed that the benefits outweigh the risks.
- Remdesivir (GS-5734) (an antiviral drug) - The available data support use under MEURI, however there should be concerted efforts made to study Remdesivir in appropriate clinical trials to assess its benefits and risks for treatment of patients with EVD.
- REGN3470-3471-3479 (a monoclonal antibody cocktail) - The data were found to be very promising and support use as another possible option under MEURI. However, there should be concerted efforts to study REGN3470-3471-3479 in appropriate clinical trials, to assess its benefits and risks for treatment of patients with EVD.
- mAb 114 (a monoclonal antibody) – mAb114 is currently in early stages of clinical development. There are data from animal models of Ebola infection showing anti-Ebola virus activity. mAb114 is being studied in a phase I dose escalation study in healthy subjects. A few Ebola-infected patients have received mAb114 in the current eastern DRC outbreak. No significant toxicities have been reported to date from the accruing use of the drug in healthy subjects and patients with EVD. However, there should be concerted efforts to study mAb114 in appropriate clinical trials to assess its benefits and risks for treatment of patients with EVD.

- Favipiravir (an antiviral drug) - The experts discussed the available data<sup>2</sup> for Favipiravir and noted considerable uncertainty as to whether it provides benefits for patients with EVD. It is important to conduct appropriate clinical trials to establish whether it provides benefits to patients or not. MEURI of Favipiravir may be considered in select circumstances where use of ZMapp or Remdesivir or REGN 3470-3471-3479 or mAb114 are not available. Its use is complicated by dosing selection<sup>3</sup> for treatment of EVD. To address the considerable uncertainty as to whether favipiravir provides benefits for patients, if it is to be used, ideally it would be utilized in selected circumstances in a randomized controlled trial that can monitor for both efficacy and safety so that adequate protections for patient safety are in place.
- The panel affirmed the importance of moving to appropriate clinical trials as soon as possible. WHO is currently developing clinical trial designs to evaluate one, two or more candidate investigational therapeutics and to assess which are beneficial to patients with EVD. WHO and partners are in active communication with product manufacturers as well as with the national authorities to expedite preparedness for clinical trials.

The expert panel recommends that access to and use of investigational therapeutics under MEURI be carefully considered for each individual patient, including for vulnerable populations such as pregnant women and pediatric patients, as appropriate given the available data. In general, the expert panel recommends that factors including disease severity, available information on risks and benefits for the investigational therapy (including any available information on adverse effects in pregnancy or pediatrics) be considered.

The topic of the use of combinations of investigational therapeutics was briefly discussed by the expert panel. A study in a non-human primate (NHP) animal model of infection is planned to evaluate for the presence of interference when a combination of investigational therapeutics are administered.

The expert panel's assessments were made based upon the currently available data as of 27 August 2018.

Patients that are receiving drug under MEURI will receive the products only after approval by relevant country authorities, including an appropriately qualified ethics committee, and after informed consent. In any setting where an investigational product is used under MEURI, there will need to be appropriate monitoring to protect patient safety as the safety and efficacy for products used under MEURI has not been established. Standardized, robust and transparent data collection on the important health outcomes is imperative. Knowledge generated through MEURI should be aggregated across patients and shared transparently and rapidly.

WHO is actively working with Health Authorities in the DRC to respond to the current Ebola outbreak to minimize harm and loss of life. All involved with the current EVD outbreak recognize that the situation can change, and WHO will re-visit these points in the future as more information becomes available or the circumstances of the outbreak in DRC change.

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<sup>2</sup> In total more than 200 EVD patients have been treated with Favipiravir, most at the JIKI doses. Designs included historical controls, and retrospective observational studies.

<sup>3</sup> The required dosing regimen is uncertain following publications indicating plasma concentrations being low in the JIKI trial. Therefore, further dose ranging studies should be performed to assess concentrations and tolerance at higher doses.

The committee will be reconvened as requested when additional data becomes available that may change the assessment.

A brief summary assessment of each drug is provided below and tables summarizing additional information and referencing currently available evidence are posted with this statement:

### **ZMapp**

There was general agreement among most participants that the available data support that the benefits of ZMapp outweigh its risks. Some noted that the Prevail II trial:

- provided the highest quality evidence available to date for efficacy for an Ebola therapy, though did not reach target enrollment.
- achieved a 91.2% posterior probability that ZMapp plus standard of care was superior to standard of care alone, but this result fell short of the 97.5% probability required to establish superiority

A few challenges were brought up regarding treatment with ZMapp including:

- the need for a cold chain
- the need for sufficient supply
- that the resources required to administer the drug to patients were a major resource commitment (e.g., long infusion time, staffing requirements)

### **Remdesivir (GS-5734)**

Among the points noted were the following:

- there are less human safety data available for GS-5734 than for ZMapp in patients with EVD, and none for efficacy in humans beyond anecdotal experience.
- that the preclinical package was sufficiently robust but that there is still uncertainty regarding the extent to which the available data from animal models of infection is likely to predict efficacy of GS-5734 in humans with EVD.
- the importance of monitoring ALT/AST as a means to minimize risk, and uncertainty regarding the capacity in the field at the current time to be able to monitor ALT/AST. Panel members expressed hope that the capacity to monitor might soon be augmented.

### **REGN3470-3471-3479**

- The results from animal models of Ebola infection are very promising and the results are similar to that observed with ZMapp.
- There is currently a limited amount of human safety data available from a phase 1 study, but findings show the drug to be generally well tolerated
- A very promising agent for further study.

### **mAb 114**

- The product is currently in early stages of clinical development.
- The data from animal models of Ebola infection including data from a NHP Ebola infection model look promising.
- A human phase 1 dose escalation study has been initiated with subjects receiving doses of up to 50mg/kg IV have been undertaken and no dose limiting toxicities have been reported in the data that are accruing.

- More than 10 Ebola infected patients have received mAb114 and reports are that they adequately tolerated the drug.

#### **Favipiravir**

- There is considerable uncertainty as to whether favipiravir provides benefit or not to patients with EVD based on the available data.
- The oral formulation of favipiravir requires less resources to administer to patients than drugs that are administered intravenously.

#### **Assessment of conflicts of interest.**

WHO requested all experts to complete the WHO DOI form and return the completed form to WHO before the meeting. Completed DOI forms were received from all participants. The following interests were declared:

1. Ross Upshur was an advisor to MSF and Public Health Agency of Canada, a participant in Compassionate Access Pilot project and a Senior Fellow with GE2P2 Global Independent Bioethics Advisory Committee. These were not deemed significant conflicts.
2. Stephan Guenther received public funds (European Commission, Germany) for research on safety and efficacy of favipiravir. This was disclosed verbally during the teleconference, and not deemed a significant conflict of interest.

#### **Note, 21 September 2018**

After the meeting, WHO received the following additional information:

1. Profs Jean-Jacques Muyembe-Tamfum and Sabue Mulangu are listed as inventors on the patent application for mAb 114, US Application No.62/087, 087 (PCT Application No.PCT/US2015/060733) related to anti-Ebola virus antibodies and their use;
2. While they are listed as inventors on this patent application, the invention in question is owned by the US Government; and
3. Profs Jean-Jacques Muyembe-Tamfum and Sabue Mulangu have not received any money for this invention, and given the low commercial value of any resulting products (limited to use during Ebola Zaire outbreaks), they consider it unlikely that they will receive any income as the inventors in the future.

Profs Jean-Jacques Muyembe-Tamfum and Sabue Mulangu were requested to update their DOI accordingly. After having reviewed the above mentioned new information and updated DOIs, WHO informed the Chair and the other experts of the MEURI group of the interests declared by Profs Muyembe-Tamfum and Mulangu, and asked the other experts to advise WHO whether or not they wish to make any changes to their conclusions. The MEURI group decided to abide by their original conclusions.

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