

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

A group of independent scientific experts convened by the WHO for the purpose of evaluating investigational therapeutics for Ebola virus disease (EVD) during the current outbreak, 17 May 2018

Experts:

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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 (MEURI¹) 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.

¹ <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 DRC outbreak with a high case fatality rate, WHO convened a meeting of scientific experts to evaluate 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 clinical trial. Committee members were provided with a framework for evaluating the evidence and translating the evidence to decision-making.

A concise summary of key points from the expert panel's deliberations 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 under MEURI in settings where ZMapp or Remdesivir are not available. However, there should be concerted efforts to study REGN3470-3471-3479 in appropriate clinical trials.
- Favipiravir (an antiviral drug) - The experts discussed the available data² 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 are not available. Its use is complicated by dosing selection³ for treatment of EVD.
- Review of mAb 114 (a monoclonal antibody) – mAb114 is currently in very early stages of development. The limited early data look potentially promising but more data are needed from clinical trials before recommending its use for MEURI.
- 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 assess which are beneficial to patients with EVD. WHO and

² 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.

³ 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.

partners are in active communication with product manufacturers as well as with the national authorities to expedite preparedness for clinical trials.

The expert panel's assessments were made based upon the currently available data as of 17 May 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 Democratic Republic of Congo (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.

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

The summary assessment of each drug is provided below:

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 drug to be generally well tolerated
- A very promising agent for further study.

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.

mAb 114

- The product is currently in very early stages of development.
- The data from animal models of Ebola infection look promising.
- The first human phase 1 study has just started and results are not yet available.

Assessment of conflicts of interest.

DOI forms were received from all participants. The DOIs were all reviewed and 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.

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