European Commission

EU-funded research on Ebola: REACTION project Questions and Answers

Brussels, 24 February 2015

The EU-funded REACTION project announced on 23 February 2015 that preliminary results from the clinical trial of favipiravir show that this antiviral drug might be effective in treating patients with early stage of Ebola disease. The results were announced by the lead investigator of clinical trial Prof Denis Malvy of the French National Institute of Health and Medical Research (Inserm) at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle.

1. **What is the REACTION project**?

REACTION is an EU-funded research project coordinated by the French National Institute of Health and Medical Research (Inserm). REACTION aims to study the feasibility, safety and efficacy of favipiravir, firstly in animals and then on patients with the Ebola virus disease. Favipiravir is an antiviral drug originally developed and licensed against influenza in Japan by Toyama Chemical/Fujifilm. It was identified by WHO as one of the potential treatments against Ebola disease that should be urgently evaluated, as it had the advantage of immediate availability and a proven safety profile that permitted to directly proceed to studies of its therapeutic effect in the outbreak zone.

The REACTION research effort is centred on three studies:

- A clinical trial of the drug's safety and efficacy in reducing mortality and viral load in patients with early Ebola disease. This study (i.e. proof-of-concept phase IIb clinical trial) is currently ongoing in three Ebola treatment centres in Guinea.
- A study of favipiravir in non-human primates with Ebola disease, in order to determine the optimal favipiravir dose and route, and to evaluate the efficacy of various administration timings (e.g. in early vs. advanced disease). The study is currently ongoing (in a high-security, BioSafety Level 4 laboratory) in Europe.
- A study of the socio-cultural repercussions of Ebola disease in Guinea. The study is currently ongoing in Guinea.

Other research institutes participating in the REACTION project include Institut Pasteur, Ecole Normale Superieure de Lyon and University Aix Marseille (France), Bernhard-Nocht-Institute for Tropical Medicine and Ruprecht-Karls University Heidelberg (Germany), University of Amsterdam and University of Utrecht (Netherlands), Public Health England (UK), and University Cheikh Anta DIOP (Senegal).

The favipiravir clinical trial in Guinea would not have been possible without the strong support, commitment and collaboration of the Guinean authorities and the Guinean people, as well as the NGOs running the Ebola treatment centres: Médecins Sans Frontières (MSF) in Guékédou, ALIMA (The Alliance for International Medical Action) in Nzérékoré, and La Croix Rouge Française in Macenta.

This concerted effort allowed the still ongoing favipiravir clinical trial to be the first that has progressed enough to provide evidence that a treatment is effective against Ebola virus disease in humans. This is all the more important as a similar clinical trial on another antiviral drug, brincidofovir, in Liberia had to be halted as of 30 January 2015 due to the declining case numbers in that country.

2. **How is the EU involved**?

Already in September 2014, the European Commission mobilised €24.4 million from Horizon 2020, the EU research and innovation programme, to support urgent Ebola research through a fast-track Emergency Procedure (IP/14/1194). REACTION is one of the five projects selected through this emergency procedure. The project was granted a total EC contribution of €2.575 million, of which €1.93 million was immediately released to support its research activities that started on 1 November 2014.

The Commission is overseeing the project to ensure that it respects all national and international ethical and regulatory requirements, and that all relevant results will be shared with the wider scientific community as soon as possible. The Commission is also facilitating the mutually beneficial collaboration between all EU-funded projects on urgent Ebola research.

3. **What are the findings? Are they valid?**

While the trial is ongoing, the new data from each patient recruited are collected and analysed at regular time intervals by the independent Data Safety and Monitoring Board (DSMB). After data from the first 80 patients (of which 11 children aged below 14 years) were analysed, the DSMB determined that:

- Favipiravir did not have any major side effects.
- Adult and adolescent patients (14 years and above) with low to moderate viral load in blood (a proxy for early disease) had a mortality rate of 15%. This was significantly better than the historical survival rate of 30% of similar patients previously treated at the same centres before the start of the trial.

- The treatment was not effective for patients which already had a high viral load in their blood (a proxy for advanced disease).

These preliminary results are based on a limited number of patients. Nevertheless, they are considered valid, as they met the *predefined* statistical criteria that indicate that the treatment reduces mortality in patients with early Ebola disease. Consequently, the independent DSMB has asked the REACTION project to already announce their findings to the wider scientific community to allow for peer review and facilitate early debate and dissemination. Meanwhile, the trial is ongoing until the initially planned sample size is reached. The additional cases recruited and treated in the trial are expected to lend further credibility to these preliminary results.

An anticipated criticism for this trial (as well all other clinical trials on Ebola treatments and vaccines currently ongoing in West Africa) is the absence of a concurrent control (placebo) group. In full awareness of this, researchers planning this and similar trials considered that the lethal nature of the Ebola disease makes it unethical to randomize patients participating in the trial and therefore deny those in the control (untreated) group the opportunity to receive a potentially life-saving treatment. Instead, they chose to treat all eligible patients with favipiravir, and compare them with a historical control group of patients treated in the same treatment centres in the period immediately before the start of the favipiravir trial (i.e. several weeks). As the standard care for patients with Ebola disease has not changed in the few weeks between this 'control' period and the study period, this allows for comparisons with a scientifically and ethically acceptable surrogate 'control' group.

4. **Do these results apply for all patients with Ebola disease**?

These preliminary results show that Favipiravir was effective in reducing mortality only in patients aged over 14 with early stages of the disease (defined as low viral load in the blood). It was not effective in patients with advanced disease (defined as high viral load in the blood).

It is not clear how well the laboratory definition of early disease (low viral load) on which the results are based corresponds with the clinical definition of early disease (less than 48 hours after the appearance of symptoms). It would not be feasible in the field to base treatment decisions on specialised laboratory tests like the viral load.

No conclusions can be drawn about its efficacy in children. Although children (younger than 14 years) are included in the clinical trial, their number was not large enough to provide reliable results during this intermediate analysis.

The additional data gathered by the ongoing trial will probably provide answers regarding the efficacy of favipiravir in children, as well as a (re-)definition of what should be considered early disease on the field.

However, even if favipiravir is finally proven effective only for early disease, this might still have a much greater general impact in the care of patients with Ebola disease:

- If patients are aware that a treatment for early Ebola disease exists, it might encourage them to present themselves for treatment earlier and thus be eligible for treatment. (Currently patients usually present themselves after the fifth day after the appearance of symptoms, when the disease is already advanced).
- It might be effective for patients with severe disease, when used in combination with other treatments. This of course will have to be proved by other clinical trials.
- Additionally, it might be used in exposed individuals that have not yet developed symptoms.

5. **What are the next steps**?

First, the publication of the findings will enable a thorough scientific discussion of the results. Based on the outcome of this discussion and potential further results, international and national regulatory agencies could proceed to approve the use of the drug.

However, based on the urgency on the situation, governments might decide to go ahead with exceptional use authorisations. It has been reported that the Guinea government may have authorised the wider use of the experimental drug in treatment centres already.

6. **What else is EU doing to support Ebola research**?

Research funding

The European Commission has promptly and strongly supported urgent Ebola research on potential treatments, vaccines and diagnostic tests with almost €140 million, leveraging an additional €100 million from the pharmaceutical industry, rapidly allocated to 13 research projects through two funding initiatives:

1. **Horizon 2020 Emergency procedure**: Directorate-General for Research & Innovation quickly mobilised €24.4 million from Horizon 2020 through an exceptional procedure launched in September 2014 to support urgent Ebola research. This is the first time this procedure has been used. The funding supports five projects addressing the development of potential treatments (three projects) and vaccines against Ebola (one project on the GSK vaccine candidate) as well as basic and translational research (one project). These projects started work as early as of 7 October 2014 (IP/14/1194).

2. Innovative Medicines Initiative **Ebola+ call:** the IMI2 "Ebola+" was launched in November 2014 to support urgent research needs for Ebola. This call has a total budget of €215 million to fund eight projects working on the development and manufacturing of vaccines (four projects covering J&J and Merck vaccine candidates), on ensuring compliance with vaccine regimens (one project), and on development of rapid diagnostic tests (three projects). Horizon 2020 contributes with €114 million, which leverages further €101 million as in-kind contributions from the pharmaceutical companies involved in the projects (IP/15/3343). The first projects started working as early as December 2014, and the hope is that they will deliver results that will contribute to tackling both the current and future outbreaks.

In addition to these newly launched initiatives, the European Commission is funding several on-going research projects that are addressing Ebola under the **EU's Seventh Framework Programme for Research and Development (FP7)**. For example, the project ANTIGONE discovered how soluble proteins produced by the Ebola virus cause damage to blood vessel walls and contribute to the internal bleeding characteristic of the disease. This finding could clear the way to produce a new treatment for Ebola in the future and could also help scientists to develop treatments for other diseases that operate the same way. More information is available online: EU research on Ebola.

Partnership with Africa

The **European Developing Countries Clinical Trials Partnership (EDCTP)** is a collaborative effort between European and Sub-Saharan African countries to develop and test promising new medical interventions for a range of poverty-related diseases such as malaria, HIV/AIDS, and tuberculosis. EDCTP recently added Ebola to the list of diseases that could be covered. A call for diagnostics is currently open.

The Commission has also urged EDCTP to mobilise funding from the Participating States to increase the EDCTP budget for 2014 and 2015 and to coordinate relevant research activities.

A coordinated global response

The current Ebola outbreak demonstrated that a rapid research response is essential. It is important to think, plan and invest in research and innovation before a health crisis occurs. This should involve in particular stronger international research funding coordination and research collaboration on both pandemic preparedness and on rapid testing of drugs and vaccines.

In this context, the Commission together with other funders recently founded the **Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)**. So far, research funding organisations from France, Spain, Canada, the U.S., Australia, Brazil, South Africa, Thailand, Korea and Mexico have joined.

This unique network – the first and only of its kind – will set up a group of research funders that could launch a coordinated emergency research response as quickly as within 48 hours in case of a significant new or re-emerging outbreak. Although not yet fully operational, the network proved instrumental in coordinating the global research effort to respond to this unprecedented Ebola outbreak.

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