

Langen, 2 October 2020

FAQ concerning the press briefing at the Paul-Ehrlich-Institut

Background information on the development of SARS-CoV-2 vaccines on the occasion of the authorisation for the first Phase-1 clinical trial of a vector vaccine against COVID-19 in Germany on 30 September 2020

Professor Dr Klaus Cichutek, virologist and president of the Paul-Ehrlich-Instituts, Federal Institute for Vaccines and Biomedicines

“The best protection from COVID-19 is an effective vaccination. At the Paul-Ehrlich-Institut, which is the competent authority for vaccines and biomedicines, we are committed to ensuring availability of safe and effective vaccines for combating the pandemic. We achieve this by research and regulation, while observing the necessary care in development and regulatory assessment

Clinical trials of vaccines are a vital step in developing vaccines. They provide information on the safety and efficacy of vaccines. We are happy to be able now to grant the authorisation of a phase 1 clinical study of a COVID vaccine developed at the German Center for Infection Research (Deutsches Zentrum für Infektionsforschung, DZIF).

We assume that a number of authorised vaccine products for European and world-wide needs will have to be made available. We also welcome the use of different technologies – vaccine platforms – for vaccine developments. The current vaccine on the basis of the MVA vaccine virus is the first vector virus for which Germany has authorised a phase 1 clinical trial.“



FAQ

1. What is the procedure for developing a vaccine against a new unknown virus?

Most vaccine developers have the experience with a particular vaccine platform i.e. vaccine technology. In developing a new vaccine on the basis of known technologies, they first establish with which components of the virus a specific and potentially protective immune reaction can be created. Once a suitable animal model is available, the protective effect against the virus will be validated as proof-of-concept. It is not until extensive studies of the possible risks have been made and until proof has been provided that the vaccine can be produced in consistently good quality that it can be tested in clinical trials of phase 1 to phase 3 on volunteers after informed consent. For this purpose, an authorisation from the competent authority in Germany, the Paul-Ehrlich-Institut as well as a favourable opinion from the competent ethics committee are required. As soon as sufficient data on the quality and manufacture as well as results from pre-clinical/non-clinical and clinical trials are available, an application for a marketing authorisation can be submitted. For Europe, the centralised marketing authorisation procedure for COVID-19 vaccines is co-ordinated by the European Medicines Agency (EMA). The assessment of the vaccine for the EMA is performed by experts from the Paul-Ehrlich-Institut and by other national medicines authorities. If the vaccine fulfils all the requirements and if its benefit outweighs its risks, a recommendation for a marketing authorisation recommendation can be pronounced. A marketing authorisation is granted by the European Commission. A vaccine product can only be marketed in the EU or the European Economic Area and used in humans after a marketing authorisation has been granted. After this has taken place, the competent vaccine commission, which in Germany is the German Advisory Committee for Immunisation Practices (Ständige Impfkommision, STIKO) at the Robert Koch-Institut, will recommend a vaccination, and, if applicable, prioritise available doses.

In view of the pandemic, the EMA has introduced a so-called “rolling review” for the submission and evaluation of COVID-related medicines. While under normal circumstances, a complete marketing authorisation application needs to be submitted before the beginning of the

assessment procedure with all the data required, the rolling review permits certain components of the authorisation application to be submitted and assessed in advance. The Committee for Medical Products for Human Use (CHMP) at the EMA, in which the Paul-Ehrlich-Institut has a member, evaluates individual data packages as soon as they have been submitted. Thus, this kind of submission does not mean that safety and efficacy data from phase 3 clinical trials are already available. They can be submitted at a later stage as additional documents. However, they must be available, and their evaluation must be completed at the time of the marketing authorisation. The marketing authorisation is granted if, based on the development and data evaluation, proof has been provided for a favourable risk/benefit ratio for the appropriate vaccine product.

2. Which role has the Paul-Ehrlich-Institut assumed in the development of vaccines in Germany?

The Paul-Ehrlich-Institut supports the work of medicines developers through early scientific advice and determines the tests and criteria required from the regulatory point of view. Clinical trials of vaccines constitute a significant step in developing vaccine products. They provide information on the safety and efficacy of vaccines. The Paul-Ehrlich-Institut is the competent authority for the authorisation of clinical trials of vaccines in Germany. Besides, it acts as the rapporteur for most of the assessment procedures of vaccines and biomedicines at the European Medicines Agency (EMA). The Paul-Ehrlich-Institut also supports a number of important bodies of the World Health Organisations, forms part of the European network of the Heads of Medicines Agencies (HMAs) and is networked in the International Coalition of Medicines Regulatory Agencies (ICMRA). With regard to product testing, it is a member of the network of the European Official Medicines Control Laboratories (OMCLs). These control laboratories are co-ordinated by the European Directorate for the Quality of Medicines (EDQM).

3. Who decides whether a vaccination authorised in Germany should be administered?

In Germany, a recommendation for a vaccination against an infectious disease is given by the German Advisory Committee for Immunisation

Practices (Ständige Impfkommission, STIKO) at the Robert Koch-Institut, in which the Paul-Ehrlich-Institut participates as a **guest** on a regular basis.

4. Which vaccine platforms are pursued in the development a SARS-CoV-2 vaccine?

According to the World Health Organisation, as per 30 September 2020, 41 vaccine candidates against COVID-19 are under clinical development. The various vaccine candidates are based on different vaccine platforms. In this context, use is made of the experience gained from the research and development of a vaccine against the MERS and SARS coronaviruses, two viruses which have been known for years. Vaccine candidates include the genetic vaccine technologies of mRNA, DNA, (messenger ribonucleic acid or deoxyribonucleic acid) vaccines, vector vaccines, genetically or synthetically engineered innocuous pathogen components (subunit vaccines, peptide vaccines), or inactivated vaccine from whole virus.

5. How does the vector vaccine MVA-SARS-2-S work?

Vector vaccines as well as mRNA and DNA vaccines contain innocuous components of the virus genome. These components contain blueprints for the surface protein of the SARS coronavirus-2 or a component of this protein. In the case of vector vaccines such as the vaccine candidate MVA-SARS-2-S currently authorised for the clinical trial, the gene material of parts of the SARS-CoV-2 coronavirus (surface protein) is inserted into the non-replication competent viral vector MVA, which is already known from the authorised smallpox vaccine Imvanex. Vector vaccines against Dengue fever and Ebola have already been authorised on a MVA basis.

After the genetic information transferred by the vaccination has reached a few body cells of the vaccinee, it is read in the cells (as well as the genetic information of the human body cells), and the spike protein of the SARS-CoV-2 is formed. The immune system reacts to this foreign protein by creating immune defences (including antibodies). If the vaccinee comes into contact with the SARS-CoV-2 pathogen again at a later stage, the immune system will recognise the spike protein and will be able to combat the virus in a targeted manner, thus, ideally preventing

Kommentiert [L1]: ...oder sollte ich schreiben „is represented with a seat“, d.h. ist das PEI in der STIKO nur Gast oder entscheidet es mit über die Impfpfehlungen., Frau Dr. Keller ist ja soweit ich weiß in der STIKO.

Kommentiert [LC2R1]: Frau Keller nimmt als aktiver Gast teil.

a COVID-19 disease or, at least alleviating its course.

6. What does a clinical trial mean?

A clinical trial serves the purpose of gaining insights into a medicinal product for human use beyond isolated cases. In general, clinical trials with the aim of a marketing authorisation for a vaccine starts with phase 1 in a small group of subjects (tolerability, safety of use, first dose finding with few healthy volunteers, < 100 trial subjects), followed by phase 2 trial, which serves dose finding and definition of a vaccine regimen (e.g. one or two vaccinations) as well as gaining insights into safety and first evidence of efficacy (several 100 to a few 1000 subjects), completed by phase 3 (statistically unambiguous proof of efficacy, documentation of the adverse effects profile) in a very large number of study participants, often several thousand or several ten-thousand clinical trial subjects.

7. Which role does the Paul-Ehrlich-Institut assume in the clinical trial of a vaccine?

The Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines validates and authorises applications for vaccines and biomedicines to be performed in Germany. A clinical trial cannot be performed in Germany before it has been authorised by the Paul-Ehrlich-Institut and has received a favourable opinion from the competent ethics committee. Since 2009, the Paul-Ehrlich-Institut is both the coordinator and an active participant in so-called "Voluntary Harmonisation Procedures" (VHPs), in which a clinical trial is validated in several European member states simultaneously. Scientific advice can currently be performed by the Paul-Ehrlich-Institut jointly with another European medicines authority (binational Advice, SNSA).

8. How long does the evaluation usually take for an application for a clinical trial on vaccines by the Paul-Ehrlich-Institut?

On average, the duration of an authorisation procedure for clinical trials is 62 days from the receipt of the application at the Paul-Ehrlich-Institut up to the authorisation. This has been the average time required for procedures from 2004 to 2018.

9. How long did it take to evaluate the application for a clinical trial of MVA-SARS-2-S by the Paul-Ehrlich-Institut?

The period required from the submission of the application through queries and validation of the answers up to the final notification concerning the application was 14 days.

10. How can the acceleration of the assessment procedure be explained – were certain aspects omitted?

All procedures related to SARS-CoV-2/COVID-19 are expedited at the Paul-Ehrlich-Institut, and processed with a larger use of staff members. Besides, multiple advice talks at short notice often take place before the application is made, and existing documents can be assessed in advance. This can expedite later authorisation processes without sacrificing the necessary care in validating the application. With regard to the use of vaccines in humans, it is required to avoid risks to a maximum possible extent while optimising the processing of an application.

11. What is the set-up of the clinical trial for the MVA-SARS-2-S vaccine?

The phase 1 clinical trial will comprise 30 healthy volunteers aged between 18 and 55 years. All subjects will receive two vaccinations at an interval of four weeks, whereby a lower dose will be applied with the first vaccination and a higher one with the second vaccination. The aim is to evaluate the safety and immunogenicity of the vaccine.

12. When can results be expected from this clinical trial?

First results may be expected after two to three months.

13. Will a clinical trial in Germany also mean a subsequent marketing authorisation for Germany?

Vector vaccines represent modern biomedicines, which can only be authorised in a European setting in the entire EU and the Economic European Area in a centralised procedure by the European Commission in coordination with the European Medicines Agency (EMA). The medicines authorities of two member states receive the rapporteurship and co-rapporteurship for processing the marketing authorisation application. The Paul-Ehrlich-Institut often assumes one of these roles in the marketing authorisation procedure.