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FAQ on the Press Briefing at the Paul-Ehrlich-Institut

Background information on the development of SARS-CoV-2 vaccines on the occasion of the authorisation of the second clinical trial of a SARS-CoV-2 vaccine in Germany

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

"The best protection against COVID-19 is a new, effective vaccination. Clinical trials of vaccines are a vital step in the development of vaccines. Such clinical trials provide information on the efficacy and safety of vaccines. In Germany, the Paul-Ehrlich-Institut is responsible for the authorisation of clinical trials for vaccines and prioritises the evaluation of applications for COVID-19 vaccines. which speeds up the procedures considerably. In addition, the institute supports vaccine developers thanks to its early scientific advice. The Paul-Ehrlich-Institut is in charge of various evaluation procedures of vaccines and biomedicines at the European Medicines agency (EMA). In addition, the institute is involved in a number of important committees of the World Health Organisation (WHO) and is part of the European network of the Heads of Medicines Agencies (HMA) as well as globally networked in the International Coalition of Medicines Regulatory Agencies (ICMRA).

FAQ

1. What is the course of development of a vaccine for a new unknown virus?

First, the pathogen is analysed and tests are performed to establish to which components of the virus the human immune system reacts in order to build up protection (including antibodies). Next, the vaccine design is developed, i.e. the experts identify which vaccine platform is suitable and which excipients are required. Animal experiments are used to test the





efficacy and tolerability of the vaccine candidate. First, extensive tests are required as well as evidence that the vaccine can be manufactured consistently in good guality. Only after that, the vaccine candidate will be tested in Phase 1 to Phase 3 clinical trials in healthy volunteers after their informed consent has been obtained. As soon as all results of the preclinical and clinical trials are available, an application for a marketing authorisation can be submitted. In Europe, the centralised marketing authorisation procedure for COVID-19 vaccines is co-ordinated by the European Medicines Agency (EMA). Experts from the national medicines agencies in Europe perform the evaluation of the vaccine for the EMA. If the vaccine fulfils all the requirements and its benefits both for the individual and public health outweigh its risks, the EMA will submit a recommendation to the European Commission after a successful marketing authorisation procedure which will last several months. The Commission will then pronounce the marketing authorisation. After that, the vaccine can be marketed and made available for human use. In Germany, a recommendation for a vaccination against an infectious disease is pronounced by the German Advisory Committee for Immunisation Practices (Ständige Impfkommission, STIKO) at the Robert Koch-Institut, in which the Paul-Ehrlich-Institut is represented as a guest.

2. Which vaccine concepts are pursued in the development of a vaccine against SARS-CoV-2?

More than 130 projects – and the number is increasing – are pursued for the development of a vaccine against COVID-19, which are based on a great variety of different approaches (vaccine platforms). These projects use the experience gained in the research and development of a vaccine against the MERS and SARS coronaviruses, which have been known for years. The most promising candidates include novel mRNA, DNA (messenger ribonucleic acids and deoxyribonucleic acid, respectively), and vector vaccines, but also other vaccine types are under development.

mRNA-/DNA- or vector vaccines contain components of the virus genome, which include the blueprints for the surface protein of Coronavirus-2 or a part thereof. After the genetic information has been inserted in a few body cells of the vaccine, it is read (just like the information of the human genome), and the appropriate surface structures (proteins) of the virus are generated. The immune system



reacts to the proteins thus formed and creates defences against them (including antibodies). If the vaccinee comes into contact with the SARS-CoV2 pathogen later, the immune system will recognise the surface structure, and will be able to combat the virus in a targeted manner, i.e. will prevent a COVID-19 infection or at least alleviate the course of the disease.

mRNA-/DNA and vector vaccines differ in the type of genetic information and the way in which this genetic information enters the cells: in the case of vector vaccines, the gene material is inserted into innocuous vector viruses which are then injected as the vaccines. The vector viruses can be attenuated vaccine viruses such as the measles vaccine virus. That way, the vaccine virus is used to insert the genetic information of the coronavirus into the cells of the vacinee. Vector viruses against Dengue fever or Ebola have already been authorised. mRNA-/DNA vaccines do not require a vector for the vaccination, i.e. a carrier virus particle. They require liquid nanoparticles (lipid droplets) to enter some of the body cells. In the case of some DNA vaccines, a short electroporation is also connected to the injection site. mRNA-/DNA vaccines have so far not been developed for the use in humans.

In addition, other vaccine concepts have been developed such as genetically engineered or synthetically produced innocuous pathogen components (subunit vaccines, peptide vaccines) or inactivated vaccines from whole virus. This shall not be presented in detail in this document.

Clinical trials (tests in humans) are currently being performed by some manufacturers in an early phase with various vaccine candidates. In Germany, the Paul-Ehrlich-Institut authorised the second clinical trial with a preventive specific mRNA vaccine against COVID-19 on10 June 2020.

3. How does the principle of an mRNA vaccine work?

mRNA is short for "messenger ribonucleic acid" - also known as messenger RNA. mRNA vaccines consist of the genetic information for one or multiple specific protein components of the viruses that are described as antigens in the vaccine. The antigens formed by some body cells after the vaccination create an immune response including the formation of protective (neutralising) antibodies. The mRNA which, in the case of SARS-CoV-2, contains the genetic information for a component



Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel Federal Institute for Vaccines and Biomedicines

> of the spike protein of the protein envelope of the virus is enveloped with specific lipid substances for the purpose of vaccine production in such a way that so-called lipid nanoparticles (LNPs) with mRNA are finally created. These LNPs are stable after the injection and can enter the cells together with the mRNA. The antigen formed by the cells with the aid of the mRNA is presented to immune cells and will create the immune response. Thus, while in the case of many conventional vaccines, the antigen itself is injected, in the case of an mRNA vaccine, the genetic information is injected, so that the body itself will produce the antigen.

4. Have any (human) mRNA vaccines been authorised yet?

No. Although there are two clinical trials with DNA and mRNA vaccines no preventive vaccines have been authorised.

5. What does a clinical trial involve?

A clinical trial serves the purpose of gaining insights in the use of a medicinal product in humans beyond the individual case. Clinical trials with the aim of a marketing authorisation of a vaccine usually start with Phase 1 in a small group of participants (tolerability, safety of the use of the medicine, first dose finding, with only few healthy volunteers, <100 participants). This is followed by Phase 2, which serves dose finding and the definition of a vaccine regimen (e.g. one or two vaccinations), as well as gaining insights into the safety and first evidence of efficacy (several 100 to a few thousand participants). In Phase 3 (statistically unequivocal evidence of efficacy, determination of an adverse effects profile) tests are conducted in a large number of participants, i.e. often thousands or tens of thousands of participants.

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

The Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines examines and authorises applications for clinical trials of vaccines and biomedicines performed in Germany. Only after the authorisation by the Paul-Ehrlich-Institut and the favourable opinion by the competent ethics committee, a clinical trial can be performed in Germany. Since 2009, the



Paul-Ehrlich-Institut has been both the co-ordinator and an active participant in so-called voluntary harmonisation procedures, in which a clinical trial is assessed simultaneously in several European member states jointly.

7. How long does the evaluation of an application for a clinical trial of a vaccine by the Paul-Ehrlich-Institut usually take?

On average, the duration of such a procedure from the receipt of the vaccine application at the Paul-Ehrlich-Institut up to the authorisation is 62 days. This is the mean value for procedures from 2004 up to and including 2018.

8. How long did it take the Paul-Ehrlich-Institut to assess the application for a clinical trial of the vaccine CVnCoV from CureVac?

From the beginning of the submission of the application to the issuance of the authorisation notification, it took nine working days.

9. How can the expedited assessment procedure be explained – were there any aspects, which were not tested?

All procedures in connection with SARS-CoV-2/COVID-19 are submitted to an expedited authorisation procedure at the Paul-Ehrlich-Institut and processed with increased staff use. The advice talks often take place at short notice before the application is submitted, and existing documents can be assessed in advance. This speeds up later authorisation processes without sacrificing the necessary care in assessing the application. What is important in the use of human vaccines is to avoid risks where possible – and at the same time, to optimise the processing work.

10. How is the clinical trial of CVnCoV designed?

The dose escalating clinical phase 1 will comprise around 168 healthy individuals between 18 and 60 years of age and cover a dosage range of between 2 μ g and 8 μ g. The aim is to determine the optimum dose and to evaluate the safety and immunogenicity.



11.When can we expect the results of this clinical trial? First results may be expected after two to three months.

12. Does a clinical trial in Germany mean that this clinical trial will also be followed by a marketing authorisation in Germany?

mRNA vaccines are modern biomedicines, which can only be authorised jointly in the EU and in the European Economic Area in a centralised procedure, co-ordinated by the European Medicines Agency (EMA) and the European Commission. The medicines authorities of two member states are given the tasks of rapporteur and co-rapporteur in such a procedure. The Paul-Ehrlich-Institut frequently assumes one of these roles in such an authorisation procedure.