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

### Background Information on the Development of SARS-CoV-2-Vaccines in View of the Authorisation of the First Clinical Trial for a SARS-CoV-2 Vaccine in Germany

#### Frequently Asked Questions

##### 1. What are the steps in developing a vaccine against a new unknown virus?

At first, the pathogen is analysed. Besides, tests are carried out to identify the components of the virus to which the human immune system reacts so that it can confer protection (including antibodies) against the virus. After that, a vaccine design is developed – which vaccine platform is suitable and which excipients are required? The efficacy and tolerability of the vaccine candidate are then tested in cell cultures (e.g. with human immune cells) and in animal experiments. Only after extensive tests and providing proof that the vaccine can be manufactured reliably in good quality it will be tested in clinical trials of Phase 1 to Phase 3 after the healthy volunteers have given their informed consent. As soon as all results of the preclinical and clinical studies are available, a marketing authorisation can be submitted. For Europe, the co-ordinating body for the marketing authorisation of COVID-19 vaccines is the European Medicines Agency (EMA). The assessment for the EMA is performed by experts of national medicines authorities in Europe. If the vaccine fulfils all the requirements and its benefits both for individuals and for public health outweigh the risks, a recommendation for a marketing authorisation will be made by the European Commission after a successful marketing authorisation procedure, which takes several months. The vaccine can then be marketed for human use. Recommendations for the vaccination against an infectious disease are given by the Standing Vaccination Committee (STIKO) at the Robert



Koch-Institute, in which the Paul-Ehrlich-Institut is represented as guest expert.

## **2. Which vaccine concepts are pursued in developing a vaccine against SARS-CoV-2?**

More than 60 projects for the development of vaccines against COVID-19 are pursued, which are based on largely differing approaches – and their number is rising. In this context, experiences of researches are used which were gained during the development of vaccines against MERS and SARS, two coronaviruses known for years. The most promising candidates include novel mRNA (messenger ribonucleic acid), DNA (deoxyribonucleic acid), or vector vaccines, but also other types of vaccines.

mRNA vaccines, DNA-vaccines, or vector vaccines contain components of the virus genome. These components comprise the genetic code for the surface protein of Coronavirus-2 or a part of this virus. After this genetic information has been inserted in a few body cells of the vaccinated person, they are read in the cells (just like the human genetic information), and the appropriate surface structures (proteins) of the virus are produced. The immune system will react to the proteins thus formed and creates immune substances (such as antibodies) against them. In the case of later contact of the vaccinated person with the SARS-CoV-2 pathogen, the immune system will recognise the surface structure and will be able to combat the virus and eliminate it.

mRNA-/DNA- and vector vaccines differ in the type of genetic information and the channels by which this genetic information is inserted in the cells. In the case of vector vaccines, the genetic material is inserted in innocuous carrier viruses, which are then injected as the vaccine. The carrier viruses can be attenuated vaccine viruses such as the vaccination measles virus. The genetic information of the coronavirus is thus inserted into the cells of the vaccinated person by means of the vaccine virus. Vector vaccines against dengue fever or Ebola have already been authorised. mRNA-/DNA vaccines do not require a vector, i.e. a carrier virus for the vaccination. They are based on liquid nanoparticles (small fatty droplets) to be able to enter body cells. For some DNA vaccines, a short subsequent electroporation procedure is performed. None of the mRNA/DNA vaccines developed for human use have so far been granted a marketing authorisation.

Other vaccine concepts include genetically engineered or synthetically produced innocuous pathogen components (sub-unit vaccines, peptide vaccines), and vaccines from inactivated whole viruses, which cannot be presented in detail in this section.

Some manufacturers are currently performing clinical studies in an early phase (first-in-man) with various vaccine candidates. On 20 April 2020, the Paul-Ehrlich-Institut authorised the first clinical trial with a preventive specific mRNA vaccine against Covid-19 in Germany.

### **3. How do the BNT162 mRNA vaccine candidates work?**

mRNA is short for messenger ribonucleic acid, also called messenger RNA. mRNA vaccines consist of the genetic information for one or more than one particular protein components of the virus. These components are called antigens in the vaccine. The antigens formed by some body cells after the vaccination convey an immune answer including the formation of protective antibodies. The mRNA, which in the case of SARS-CoV-2 contains the genetic information for a component of the spike protein of the protein envelop of the virus is enveloped with particular lipid substances for vaccine production, so that, finally, so-called lipid nanoparticles (LNP) are formed, which contain mRNA. These LNP are stable after injection and able to enter the cells together with the mRNA. The antigen formed with the aid of the mRNA is presented to immune cells and will convey an immune response. Thus, while many conventional vaccines are based on an injection of the antigen itself, in the case of mRNA vaccines, it is the genetic information, which is injected, enabling the body itself to form the antigen.

### **4. Have any (human) mRNA vaccines been granted a marketing authorisation?**

No. Although clinical trials with DNA and mRNA vaccines are ongoing, no preventive vaccines in these categories have so far been authorised.

### **5. What does a clinical trial involve?**

Clinical trials serve to obtain insights into a medicinal product about the use in humans beyond isolated cases. A clinical trial with the aim of

obtaining a marketing authorisation for the vaccine usually starts with Phase 1. This involves a small cohort of healthy volunteers (<100), (tolerability, safety of use, first dosage finding tests. Next, Phase 2 is performed, which serves to find the appropriate dosage and to define a vaccination regimen (e.g. one or two vaccinations), and to gain insights into the safety and first evidence of the efficacy (several 100 up to a few 1000 participants). Finally, Phase 3 follows (statistically unambiguous evidence of efficacy, identification of the adverse events profile) on a large number of participants, often thousands of healthy volunteers or patients.

**6. Which role does the Paul-Ehrlich-Institut play in the clinical trials for 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. A clinical trial requires the authorisation from the Paul-Ehrlich-Institut and a favourable opinion by the competent ethics commission before it can be performed.

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

On average, the procedure from the receipt of the application at the Paul-Ehrlich-Institute up to the authorisation takes 62 days. This is the average for all procedures performed from 2004 up to and including 2018.

**8. How long did it take for the application for the clinical trial for the vaccine BNT162 from BioNtech to be assessed by the Paul-Ehrlich-Institut?**

5 working days were required from the day of filing the application to the production of the authorisation notification.

**9. How can the accelerated authorisation procedure be explained? Are there any aspects, which were not assessed in this case?**

All procedures in connection with SARS-CoV-2/Covid-19 are subjected to the accelerated procedure and processed with an increased number of

staff members. Multiple scientific advice activities often take place prior to the submission of the application at short notice, and existing documents can be assessed in advance. This helps accelerate later application processes without risking any losses with regard to the required care in assessing an application. A requirement for the use of vaccines in humans is to avoid risks as far as possible while optimising the processing of the application.

**10. When can the results of this clinical trial be expected?**

First results could be expected possibly after 2-3 months.

**11. Will a clinical trial in Germany also be followed by a marketing authorisation of Germany?**

mRNA vaccines are modern biomedicines which can only be authorised jointly with in the EU and the European Economic Area in a centralised marketing procedure by the European Commission co-ordinated by the European Medicines Agency (EMA). Two member states can be chosen as rapporteur and co-rapporteur for preparing the assessment report. The Paul-Ehrlich-Institut often assumes such a role in the marketing authorisation procedure.