Authorisation of the second Clinical Trial of a Covid-19 Vaccine in Germany

Press Briefing of the Paul-Ehrlich-Institut, Federal Institut for Vaccines and Biomedicines

17 June 2020
Agenda Press Briefing

- Welcome, role of the Paul-Ehrlich-Institut (PEI) in vaccine regulation
- Basic principles of clinical trial authorisation (PEI)
- Study planning (presentation CureVac)
- Prospects for the future (PEI)

**PRESENTERS**

- Dr Franz Werner-Haas, CEO, COO, CureVac
- Dr Mariola Fotin-Mleczek, CTO, CureVac
- Professor Dr Klaus Cichutek, president of the Paul-Ehrlich-Institut
Scientific Advice from Paul-Ehrlich-Institut accelerates Covid-19-RNA Vaccine Development

- National scientific advice (innovation@pei.de)
  Early advice on the entire route of development

- Guide to scientific advice from EMA (European Medicines Agency)
  In a later phase of development -> preparation for an authorisation application

- Research at the Paul-Ehrlich-Institut
  Studies concerning the development of the safety and the protective effect of vaccine platforms in the laboratory

- International harmonisation: EMA, WHO, ICMRA, HMA, …

- Policy advice, public relations, …
The Paul-Ehrlich-Institut protects Patients and supports the Medicines Development.

- **Discovery**
- **Non-clinical tests**
- **Manufacture**
- **Clinical trials**
- **Standard therapy/prevention**
- **Pharmacovigilance**
- **Experimental testing & official batch release**
- **Authorisation of the clinical trial**
- **Inspections and Support of federal state / Support from EMA inspections**
- **Risk co-ordination**

**Authorisation:** European Commission/PEI

*PEI scient. advice/innovation office*

*EMA Scientific Advice*

*Additional benefit (advisory function)*
Regulatory Activities (up to 5 June 2020)

Scientific advice, Paul-Ehrlich-Institut (PEI)
- 15x advices by PEI on COVID-19 vaccines
- 20x advices by PEI on COVID-19 therapeutics
- 14x Emergency task force EMA/PEI participations
- 3x global telephone conferences with FDA/WHO
- including binational scientific advice (SNSA)

Authorisation of clinical trials by the Paul-Ehrlich-Institut
- 2x authorisations, human vaccine specific
- 2x authorisations, human vaccine non-specific
- 2x authorisation, reconvalescence plasma
- 5x authorisations, mAb
INTERNATIONAL NETWORKING

ICMRA – International Coalition of Medicines Regulatory Agencies
- Telephone phone conferences (TCs) every 2 weeks

WHO Organisations
- Prioritising of vaccines
- Animal studies
- Clinical trial design
- Reference material for assays

HMA – Heads of Medicines Agencies in Europe
- Business Continuity
- Supply shortages (availability)

EMA – European Medicines Agency
- Accelerated authorisation with rolling review
- Business continuity

Vaccines developments world-wide
- >130 vaccine projects
- 10 Covid-19 vaccines in clinical trials
- 2 Clinical trials Phase II/III authorised (USA, UK)

As per 2 June 2020
<table>
<thead>
<tr>
<th>Platform</th>
<th>Type of candidate vaccine</th>
<th>Developer</th>
<th>Current stage of clinical evaluation</th>
<th>Same platform for non-Coronavirus candidates</th>
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<tbody>
<tr>
<td>Non-Replicating Viral Vector</td>
<td>Adenovirus Type 5 Vector</td>
<td>CanSino Biological Inc./Beijing Institute of Biotechnology, China</td>
<td>Phase II ChiCTR2000031781 Phase I ChiCTR2000030906</td>
<td>Ebola</td>
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<td>RNA</td>
<td>LNP-encapsulated mRNA</td>
<td>Moderna/NIAID, U.S.A.</td>
<td>Phase 1 NCT04283461</td>
<td>multiple candidate vaccines</td>
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<td>Inactivated</td>
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<td>Wuhan Institute of Biological Products / Sinopharm</td>
<td>Phase 1/2 ChiCTR2000031809</td>
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<td>Beijing Institut of Biological Products / Sinopharm</td>
<td>Phase 1/2 ChiCTR2000032459</td>
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<td>Inactivated</td>
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<td>Sinopharm</td>
<td>Phase 1/2 NTC04383574 NTC04352508</td>
<td>SARS</td>
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<td>Inactivated</td>
<td>Inactivated</td>
<td>Institute of Medical Biology / Chinese Academy of Medical Sciences</td>
<td>Phase 1</td>
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<td>Non-Replicating Viral Vector</td>
<td>ChAdOx1-5</td>
<td>University of Oxford / Astra Seneca / Serum Institute of India</td>
<td>Phase 1/2 NCT04324606</td>
<td>MERS, Influenza, TB, Chikungunya, Zika, MenB, Plague</td>
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<td>Protein Subunit</td>
<td>Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M</td>
<td>Novavax, U.S.A.</td>
<td>Phase 1/2 NCT04368988</td>
<td>RSV, CCHF, HPV, VZV, EBOV</td>
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<td>RNA</td>
<td>LNP-encapsulated mRNA, saRNA</td>
<td>BioNTech, Germany</td>
<td>Phase 1/2 2020-001038-36 NCT04368728</td>
<td>multiple candidate vaccines</td>
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<tr>
<td>DNA</td>
<td>DNA plasmid vaccine</td>
<td>Inovio Pharmaceuticals, U.S.A.</td>
<td>Phase 1 NCT04336410</td>
<td>Lassa, Nipah , HIV, HPV, Filovirus, ZIKA, Hepatitis B, Cancer indications</td>
</tr>
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Authorisation of a Phase1/2 Clinical Trial of a Vaccine in Germany

Prerequisites

Vaccine platform

- Unmodified RNA (not self-amplifying)
- Clinical experience with preventive RNA vaccines
e.g. preclinical/clinical trials with a rabies RNA vaccine

Choice of the pathogen component conferring immune protection

- Antigen (active substance in the vaccine)
  - Genome in the form of RNA
    with blue-print of the CoV-2 S-protein
  - Stabilising pre-fusion conformation of the spike protein
Authorisation of a Phase1/2 Clinical Trial of a Vaccine in Germany
Manufacture (GMP), Quality

- Quality assured RNA manufacture
  \((In-vitro\) transcription with DNA as the template)
  - Manufacture on a large scale (up-scaling) for combined Phase 1/2

- Formulation of the vaccine and filling
  - Chemically non-modified RNA
    + LNP (lipid nanoparticles, water-soluble)

- Quality and batch testing at the manufacturer
  - Identity of the RNA
  - Specifications: Portion of RNA in the vaccine, RNA integrity
Authorisation of a Phase 1/2 Clinical Trial of a Vaccine in Germany
Pre-clinical Studies/Reference: Rabies-RNA Vaccine

- Pharmacology and pharmacokinetics (cell culture)
  - Formation of the required antigen (full-length spike protein)
- Immunogenicity, dose, vaccination regimen in the animal model (mouse)
  - Generation of the immune response against the spike protein of CoV-2
  - Dosing (amount of RNA per dose)
  - Vaccination regimen (vaccination: once or twice, time interval?)
- Toxicology in the case of repeated vaccine release (rat)
  - Platform data (rabies vaccine)
  - Test for organ damage, local tolerability
- Biodistribution
Phase 1 testing:
- Step-by-step increase of doses (3 dose stages; 144 vaccinees receiving verum, 24 vaccinees receiving placebo)
- Two age-groups: 18-40 years and 41-60 years
- No inclusion of elderly or vulnerable persons
- 168 persons (seronegative and seropositive)
- Duration: 15 months

Aim: safety, reactogenicity (tolerability), immunogenicity
- Neutralising antibodies, binding antibodies
- Physiological reactions (reactogenicity, tolerability)
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Possibilities of expedited Covid-19 Vaccine Developments while maintaining the required Care

- Pivotal (essential) pre-clinical trials in cell culture and in the animal
  - Immunogenicity, first dose finding, repeated administration (mouse)
  - Referencing to comparable vaccine products of the same platform
- Non-clinical trials in parallel to the first clinical trial
  - Intolerability (toxicity) in the case of repeated administration (rat)
- Phase 1 clinical trial
  - Tolerability, first dose-finding,
    Vaccination twice, if required; healthy adults 18 to 60 years of age in combination with
- Phase 2 clinical trial
  - Safety, exact dose and determination of vaccine regimen
- Combined Phase 2/3 trial with > 10,000 persons
Preventive Measures to reduce theoretical Risks associated with Covid-19 Vaccine Developments

Theoretical risks

- Generation of infection-reinforcing antibodies
  - Reinforced infectious disease after the vaccination
- Th2 polarisation of the immune response with consequential organ damage
  - Cytokine profile dependent

Preventive measures

- Th1 polarising vaccine platform (RNA)
- Prefusion conformation of the spike protein antigen
- Determination of the cytokin profile and toxicology in the animal
- Determination of the cytokin profile of the vaccinee
- Targeted adverse effect analysis
Today’s Paul-Ehrlich-Institut
Our Focus is on Health!