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Langen, Germany

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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

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Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

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)

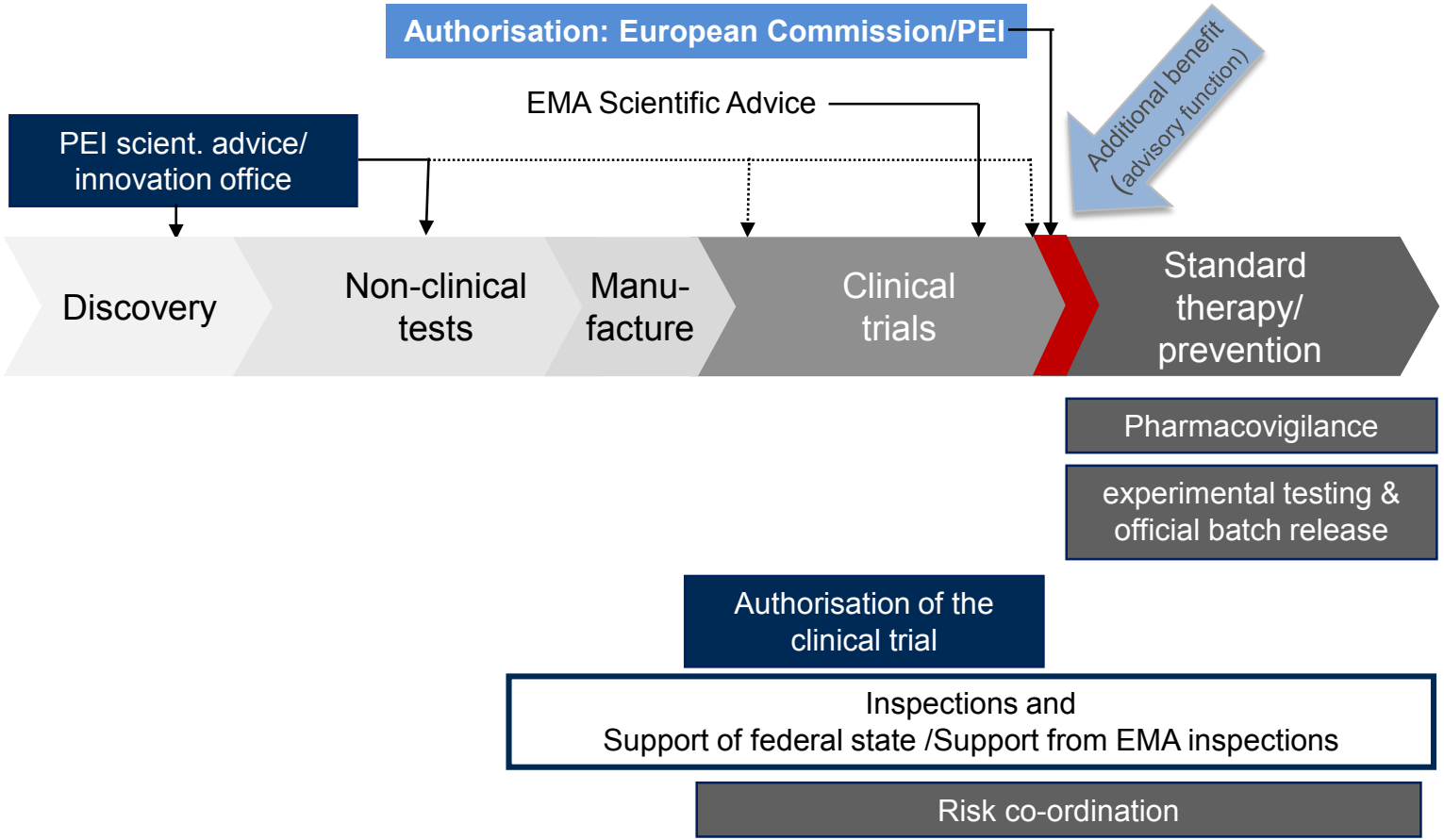
PRESENTERS

- 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 scientifc 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



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

Regulatory Activities (up to 5 June 2020)

INTERNATIONAL NETWORKING

ICMRA – International Coaliton 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

On-going Clinical Trials world-wide: Preventive SARS-CoV-2 Vaccines

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

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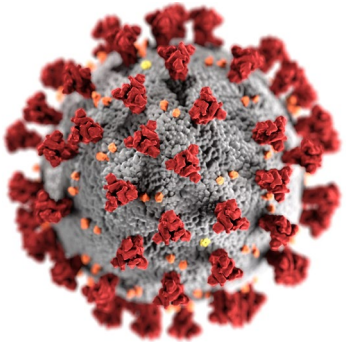
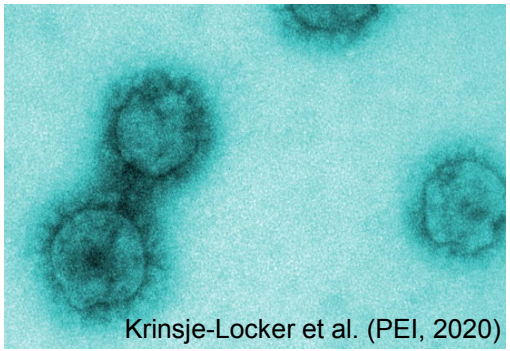
Authorisation of a Phase1/2 Clinical Trial of a Vaccine in Germany
Prerequisites



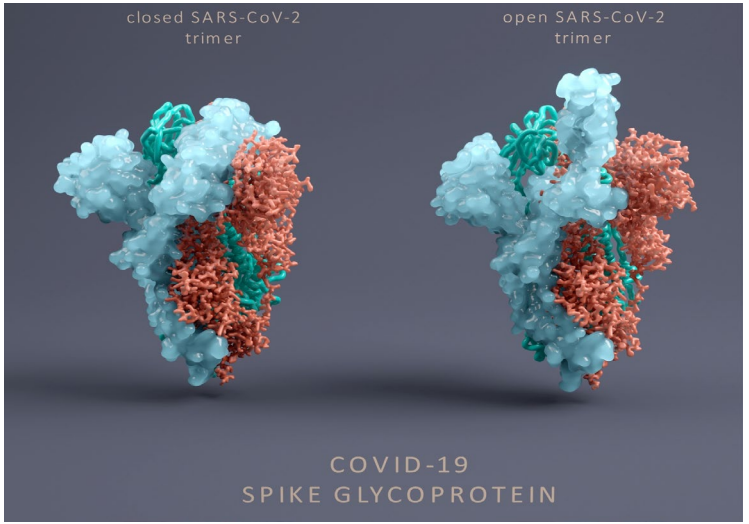
- Vaccine platform
  - Unmodified RNA (not self-amplifying)
  - Clinical experience with preventive RNA vaccines
    e.g. preclinical/clinical trials with a rabies RNA vaccine

- 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


Krinsje-Locker et al. (PEI, 2020)

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

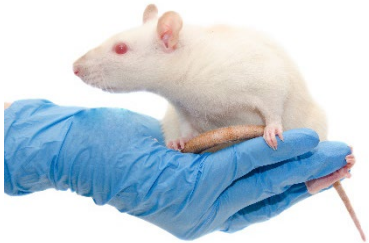


Authorisation of a Phase1/2 Clinical Trial of a Vaccine in Germany
Pre-clinical Studies/Reference: Rabies-RNA Vaccine

- 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 regiment (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

Authorisation of a Phase1/2 Clinical Trial of a Vaccine in Germany
Special Characteristics of Clinical Trials

- 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 maintaing 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!