Authorisation of a Clinical Trial Phase I of a Vector Vaccine against COVID-19

Press Briefing of the Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines
2 October 2020

Klaus Cichutek et al.
Paul-Ehrlich-Institut
Press briefing DZIF/IDT
October 2nd 2020
Langen
Authorisation of a Phase 1 Clinical Trial (FiH) of a COVID-19 Vector Vaccine in Germany (German Center for Infection Research, DZIF)

- Welcome, role of the Paul-Ehrlich-Institut (PEI) in vaccine regulation
- COVID vaccine candidates, clinical trial authorisation
- Vaccine development and manufacture
- Trial design (DZIF Presentation)
- Outlook
- Q & A
Podium Participants

- **Professor Marylyn Martina Addo**, Head of Infectiology at the University Hospital Hamburg-Eppendorf
- **Professor Gerd Sutter**, full Professor for Virology, Ludwig-Maximilians-Universität München
- **Dr. Andreas Neubert**, Chief Scientific Officer, IDT Biologika
- **Professor Klaus Cichutek**, President, Paul-Ehrlich-Institut (host)
The Paul-Ehrlich-Institut protects Patients and supports Biomedicines’ Development all along their Life Cycle

- Marketing authorisation by EC or PEI
- EMA Scientific Advice
- HTA Additional use (advisory role)
- Pharmacovigilance
- Experimental testing and Official batch release
- Clinical trial authorisation
- Inspections and inspections support for German federal state authorities and EMA
- Risk coordination

- Discovery
- Non-clinical trials
- Manufacture
- Clinical trials
- Standard therapy/prevention

- PEI Scientific advice/innovation office

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Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial

Vaccine Characteristics

- Selection of a vaccine platform: non-replication competent vector vaccine
  - MVA vaccine virus (Imvanex-like)
  - Existing clinical experience with MVA-based vector vaccines
    and authorised vector without foreign gene

- Identification of the pathogen component providing immune protection
  - From MERS Corona virus research: MERS-CoV spike protein
  - Full-length spike protein is the antigen (vaccine’s active ingredient)

- No modification of the genetic information (blue-print) for antigen generation
Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Manufacture (GMP), Quality Data

- Quality-assured vaccine vector manufacture in cell culture at IDT Biologika
  - Larger-scale manufacture (up-scaling) for Phase 1 trial
- Vaccine formulation and filling
- Batch testing at manufacturing site
  - Identity of vector and antigen gene
  - Vector titer in pre-defined volume,
  - Testing of two dose strengths
    - Low dose: $1 \times 10^7$ IU/ml,
    - High dose: $1 \times 10^8$ IU/ml
  - Low content of cell components
Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Pre-clinical Data

- Immunogenicity and dose studies in the animal model (mouse)
  - Generation of immune response against CoV-2 spike protein
  - Optimum dosage (amount of vector particles per dose)
  - Vaccine regimen (vaccination once or twice, interval?)

- Toxicology (rat, rabbit) after repeated vaccine administration (ongoing)
  - Platform data, MERS-MVA vaccine
  - Test for organ damage, local tolerability

- Pharmacology and pharmacokinetics (cell culture)
  - Generation of the required antigen (full-length spike protein)
Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial

Aim of the Clinical Trial

- **Aim:** Safety, tolerability, reactogenicity, antibody induction
  - **Immunogenicity:** Generation of immune response against the spike protein dosage (amount of vector particles per dose)
  - **Safety (risks):**
- **Pharmacovigilance, reactogenicity**
  - General tolerability (fever, headache, malaise,...)
  - Local tolerability (redness of the skin, haematoma,...)
- **Pharmacology and pharmacokinetics, immune response**
  - Antibody identification
  - Neutralising vs. binding antibodies
  - Balance of immune response (Th1 vs. Th2)
- **Approx. 30 persons, no control arm**
Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Special Characteristics of the Clinical Trial

- Healthy adults 18 to 55 years
  - Two i.m. vaccinations in 28 days interval
  - 15 persons in low dosage group (1x10^7 IU/ml),
  - 15 persons in high dosage group (1x10^8 IU/ml)
- Cytokine profile in the blood
- Neutralising antibodies, binding antibodies
- Additional data on ADE and ERD in animal model will be submitted before starting Phase 2/3
Challenges in Development and Regulation of COVID-19 Vaccine

- Welcome, role of the Paul-Ehrlich-Institut (PEI) in vaccine regulation
- Covid vaccine candidates, clinical trial authorisation
- Development and manufacture
- Trial Design (DZIF Presentation)
- Outlook
Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated.

Inactivated adjuvanted Whole-virus vaccine

Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated.

Inactivated Vector vaccine

Rec. Protein-Impfstoff: Receptor binding domaine

Rec. Protein vaccine (Sub-unit vaccine): Full-length spike protein

Live vaccine, attenuated

Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture.

Live vaccine, attenuated

SARS-CoV-2

Spikeprotein

Receptor binding domain (RBD)

Virus-like Particle (VLP)

RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs)

DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promotor

Replication competent vector vaccines can propagate to some extend in the vaccinee’s cells and express the spike protein there.

Replication-competent Vector vaccine

Non-replication competent Vector vaccine

RNA vaccine (Lipid nano particles)

Non-replication competent vector vaccines cannot propagate in the vaccinee’s cells but express the spike protein there.

DNA vaccine (Electroporation)
<table>
<thead>
<tr>
<th>Institution/Manufacturer</th>
<th>Vaccine platform</th>
<th>Type of candidate vaccine</th>
<th>Number of doses</th>
<th>Timing of doses</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Oxford/AstraZeneca</td>
<td>Non-Replicating Viral Vector</td>
<td>ChAdOx1-S</td>
<td>1</td>
<td></td>
<td>IM</td>
</tr>
<tr>
<td>Biontech Inc./Beijing Institute of Technology</td>
<td>Non-Replicating Viral Vector</td>
<td>Adenovirus Type 5 Vector</td>
<td>1</td>
<td></td>
<td>IM</td>
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<tr>
<td>Sanya Research Institute</td>
<td>Adeno-based (rAd26-S+rAd5-S)</td>
<td>2</td>
<td>0.21 days</td>
<td>IM</td>
<td></td>
</tr>
<tr>
<td>Sinovac Biotech</td>
<td>Non-Replicating Viral Vector</td>
<td>Ad26COVS1</td>
<td>2</td>
<td>0.56 days</td>
<td>IM</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Inactivated</td>
<td>2</td>
<td>0.14 days</td>
<td>IM</td>
<td></td>
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<tr>
<td>Institute of Biological Sciences/Sinopharm</td>
<td>Inactivated</td>
<td>2</td>
<td>0.21 days</td>
<td>IM</td>
<td></td>
</tr>
<tr>
<td>Institute of Biological Sciences/Sinopharm</td>
<td>Inactivated</td>
<td>2</td>
<td>0.21 days</td>
<td>IM</td>
<td></td>
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<tr>
<td>China/NIAID</td>
<td>RNA</td>
<td>LNP-encapsulated mRNA</td>
<td>2</td>
<td>0.28 days</td>
<td>IM</td>
</tr>
<tr>
<td>BioNTech/Pharma/Pfizer</td>
<td>RNA</td>
<td>3 LNP-mRNAs</td>
<td>2</td>
<td>0.28 days</td>
<td>IM</td>
</tr>
<tr>
<td>Inovio</td>
<td>Protein Subunit</td>
<td>Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M</td>
<td>2</td>
<td>0.21 days</td>
<td>IM</td>
</tr>
<tr>
<td>Zhifei Longcom Biopharmaceutical/Institute of Biochemistry, Chinese Academy of Sciences</td>
<td>Protein Subunit</td>
<td>Adjuvanted recombinant protein (RBD-Dimer)</td>
<td>2 or 3</td>
<td>0.28 or 0.28,56 days</td>
<td>IM</td>
</tr>
<tr>
<td>mRNA</td>
<td>RNA</td>
<td>mRNA</td>
<td>2</td>
<td>0.28 days</td>
<td>IM</td>
</tr>
</tbody>
</table>

### 41 x Covid-19 Vaccine Candidates in Clinical Trials

(30 September 2020; WHO landscape)

- 10x in Phase 3
- 2x in Phase 2
- 11x in Phase 1/2
- 17x in Phase 1

- Phase 3 trials
  - 4x vector vaccines
  - 3x inactivated vaccines
  - 3x RNA vaccines
  - 2x rec. protein vaccines
COVID-19 vaccine development

Design and exploratory preclinical

Process development, preclinical, toxicology studies

Clinical trials

Phase III

Phase I/II

Overlapping clinical phases

Production at risk

Regulatory review

FDA, EMA etc.

Pre-existing from SARS-CoV-1 and MERS CoV

Partially pre-existing and parallel development

IND submitted

BLA submitted

Review on a rolling basis? EUA?

months

months

months

10 months to 1.5 years
COVID-19 Impfstoffentwicklung
Schneller, aber sicher


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Paul-Ehrlich-Institut,
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Langen
PEI COVID-19 Regulatory Activities

Scientific advice PEI
- 25x PEI scientific advices on COVID-19 vaccines
- 31x PEI scientific advices on COVID-19 therapeutics incl. binational scientific advices (SNSA)
- 10x Emergency Task Force EMA/PEI participations / vaccines
- 12x Emergency Task Force EMA/PEI participations / therapeutics

Clinical trial authorisations by PEI
- 6x COVID-19 vaccines
- 2x non-specific immunostimulating human vaccines
- 6x convalescent plasma
- 12x monoclonal antibodies (mAb)
- 2x Advance therapy medicinal products (ATMP)

Batch release testing, pharmacovigilance, inspections, assessment of centralised marketing authorisation applications, diagnostics performance evaluation, research on vaccine platforms

by 28 August 2020
Paul-Ehrlich-Institut’s support to Covid-19 Vaccine Development

- ICMRA (regulatory convergence)
  - 10x global TCs with US-FDA/WHO/ICMRA
- WHO Strategic Advisory Group of Experts (SAGE) on Immunization; Covid-19 vaccines Working Group
- WHO Expert Committee for Biological Standardisation (ECBS)
- WHO Blueprint Committees
- Daily and weekly reports on Covid vaccine development to the German Federal Ministry of Health (BMG)
- Working Group of Competence and Treatment Centers for highly contagious and life-threatening diseases (STAKOB)
- Vaccination plan/ vaccine availability BMG, federal states, RKI, PEI
- Expert review activities for the Federal Ministry of Research and Education (BMBF)
- No participation in negotiations on “advance purchase agreements”

As per 28/08/20
Summary: Challenges in Development and Regulation of Covid-19 Vaccines

- Status of development: 41 clinical trials, out of these 12 in Phase 2 & 3, all technologies at the trial stage
- Acceleration of development: Non-clinical trials in parallel with trials, combinations of Phases 1/2 and 2/3
- PEI research contributions: Lab research on vaccine models
- Biomedical therapeutics: Small Molecules, convalescent plasma, Hyper-Immunoglobulins, neutralising antibodies, immunomodulating antibodies
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

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