Whole virion inactivated vaccine with adjuvant

EQUIVAX

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Natalie Mandel, Chief Financial Officer
1. Describe and discuss the pro and cons of your vaccine construct, including cold-chain and cost issues.
2. Describe and discuss the pro and cons of route of administration including vaccine delivery devices, if applicable.
3. Briefly describe your proposed preclinical toxicology, immunology and pre-clinical efficacy studies.
4. Present your Target Product Profile.
5. Present an abbreviated Phase 3 trial design including the following elements:
   a. Population to be enrolled with inclusion and exclusion criteria
   b. Estimated duration of the trial
   c. Immunization schedule
   d. Primary outcome measure and how the outcome will be determined/measured
   e. Secondary outcome measures (up to 3) and how they will be determined/measured
   f. Briefly describe immunology studies and when samples will be collected
   g. Briefly describe how you will determine sample sizes for primary efficacy and safety outcomes.
6. Present an abbreviated post-marketing phase 4 study design, proposing outcomes to be explored.
7. After your vaccine is approved, assume you are members of the WHO committee that will determine who should first receive the vaccine when becomes available. Please describe and defend your top five populations in low- and middle-income countries (who, and in what situation).
Suggestions

- 35-50 slides, 45 min presentation, 15 min Q&A
- Topic 3 includes toxicology studies/plans to test on animals before clinical trials
- Can look up Phase 3 trials from Pfizer and Moderna on Internet
  - Can go to summary for similar info about phase 3 trial plan
  - Current adjuvant for Sinopharm is alum, but can use another one if we want
- Go to clinicaltrials.gov in the Covid vaccines section to find the trials going on worldwide
  - Filter them by the ones in phase 3 - use them for ideas
  - NYT Covid vaccine tracker also has concise updates on vaccines in trials
    - Several inactivated ones (two from China, one in early development in India)
- Phase 4:
  - Look at safety questions too infrequent to be answered in phase 3, and for groups not studied in phase 3 (e.g. pregnant women - and following outcomes on vaccinated pregnant women)
  - Ex: immunogenicity study of a specific group over 10 years to study if antibodies persist - but you have to justify why you are doing this
Disclosures

None
“At EQUIVAX, we believe the future of healthcare lives at the intersection of medicine and public health. Through a combination of education, research, and practice, EQUIVAX demonstrates its explicit commitment to understanding and eliminating health disparities worldwide through the development of cost-effective, quality, and equitable vaccinations.”
In line with the EQUIVAX mission statement, our target audience includes stakeholders, corporate investors, scientists, public health officials as well as the lay population.
Whole virion inactivated vaccine with adjuvant

What is it?

- **Inactivated vaccine**: vaccine that uses the killed version of the germ that causes a disease.
  - Made by exposure of virulent virus to chemical or physical agents (i.e. beta-propiolactone) in order to destroy infectivity while retaining immunogenicity.

- **Adjuvant**: adjuvants are ingredients added to vaccines to create a strong immune response (i.e. aluminum salts)
  - More local and systemic responses than non-adjuvanted vaccines
WHAT IS AN ADJUVANT, AND WHY ARE THEY USED IN VACCINES?

Talking about Vaccines with Dr. Stanley Plotkin
Pros

- Vaccine production is relatively straightforward to achieve
- Inactivated viral vaccines have a heightened safety aspect as compared to live attenuated viral vaccines.
  - The fact that the pathogen is completely inactivated directly negates reversion to a virulent phenotype within the vaccine recipient.
  - The improved safety profile of inactivated vaccines entails that they are also suitable for the rapidly increasing group of immunocompromised individuals
- Many are produced via virus growth on continuous cell lines
  - Infinite cell growth and division
  - Easy isolation of mutant cells
  - Reduced production costs
  - Straightforward upscaling
- Fewer regulatory hurdles for licensure
<table>
<thead>
<tr>
<th>Company and country</th>
<th>Vaccine name</th>
<th>Number of doses</th>
<th>Approval and registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinovac Biotech, China</td>
<td>---</td>
<td>2</td>
<td>Ahead of Phase II trial it is offered to essential workers and other high-risk people of the Chinese town of Jiaxing for about 30 €/dose</td>
</tr>
<tr>
<td>Beijing Institute of Biological Products and Sinopharm,</td>
<td>BBIBP-CorV</td>
<td>2</td>
<td>Limited approval for Chinese health care workers and ahead of Phase III trial. This vaccine has been approved by United Arab Emirates on the basis of preliminary data showing that it is 86% effective.</td>
</tr>
<tr>
<td>China</td>
<td></td>
<td></td>
<td>Limited approval for Chinese health care workers and soldiers ahead of Phase III trial.</td>
</tr>
<tr>
<td>Wuhan Institute of Biological Products, and Sinopharm,</td>
<td>---</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bharat Biotech, India</td>
<td>COVAXIN</td>
<td>2</td>
<td>The Phase III trial with 26 000 volunteers is expected to close in February 2021.</td>
</tr>
</tbody>
</table>
Pros

- No secondary mutations can lead to reversion to virulence so disease can’t occur and the vaccine is not transmissible.
- Inactivated vaccines usually don’t require refrigeration, and they can be easily stored and transported in a freeze-dried form, which makes them cheap and easily accessible to people in developing countries.
- BIBP-CorV can be transported and stored at normal refrigeration temperatures (2-8 degrees Celsius).
  - A large amount can be produced: Sinopharm said it may have the capacity to produce more than 1 billion doses in 2021
Cons

- These vaccines take longer to culture and produce than other vaccine types
  - Chemical treatment may reduce efficacy of the vaccine
- Protection from this vaccine type may be weaker, so a larger amount of antigen is needed to produce a satisfactory immune response
  - People may need multiple booster shots
Cons

- Adding an adjuvant and the need for multiple doses raises production and vaccine cost
- Previous exposure could compromise the immune response
- Complete inactivation MUST be ensured
  - The Cutter Incident
  - RSV
- There is an increased risk of allergic reactions due to the presence of large amounts of unrelated structural antigens of microbes.
Pre-Clinical Studies
Highlights

- An inactivated SARS-CoV-2 vaccine candidate, EQUIVAX, is developed.
- EQUIVAX induces high levels of neutralizing antibodies titers in animal models.
- Two-dose immunization with 2 mg/dose EQUIVAX efficiently protects rhesus macaques.
- EQUIVAX is efficiently produced, genetically stable, and seems to be safe in animals.
Initial immunogenicity studies evaluated EQUIVAX in mouse models. Mice received various doses (2, 4, or 8 mg/dose) of vaccine mixed with aluminum hydroxide adjuvant in a one, two or three dose series. Serum neutralizing antibody levels were collected at predefined intervals to determine immunogenicity.

We then expanded the evaluation to include different animal models including rabbits, guinea pigs, and rats. The results demonstrated that EQUIVAX has good immunogenicity, and the seroconversion rate reached 100% at day 21 after immunization in all animal models.
Protection in a Nonhuman Primate Animal Model

Recent studies have shown that SARS-CoV-2-infected rhesus macaques developed pulmonary infiltrates and histological lesions.

We evaluated the immunogenicity and protective efficacy of EQUIVAX in rhesus macaques.
Immunogenicity and Protective Efficacy of EQUIVAX in Nonhuman Primates (NHPs)

(A) Experimental strategy.
NHP Studies

Macaques were immunized twice with 2 mg/dose (n = 4) or 8 mg/dose (n = 4) of EQUIVAX or placebo (n = 2). NAb titers were measured.

The protective efficacy of EQUIVAX against SARS-CoV-2 challenge at 10 days after second immunization was evaluated in macaques.

https://doi.org/10.1016/j.cell.2020.06.008
NHP Studies

Changes in temperature (C) were recorded. Viral loads in throat (D) and anal swabs (E) obtained from macaques at 3, 5, and 7 days post inoculation.
NHP Studies

Viral loads in all seven lung lobes collected from all macaques at day 7 post inoculation were determined by real-time PCR.

- Data points represent individual macaques
- Asterisks indicate significance: **p < 0.01
- Dotted lines indicate the limit of detection

https://doi.org/10.1016/j.cell.2020.06.008
NHP Studies

Histopathological changes in lungs of macaques at day 7 post inoculation. All macaques received vaccination showed normal lung with focal mild interstitial pneumonia in few lobes.

https://doi.org/10.1016/j.cell.2020.06.008
## NHP Studies: Results Summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage Range</strong></td>
<td>4–8 μg (i.m.)</td>
</tr>
<tr>
<td>Neut. titre after prime</td>
<td>1:100 range⁺</td>
</tr>
<tr>
<td>Neut. titre after boost</td>
<td>1:200 range⁺</td>
</tr>
<tr>
<td>T Cell Response</td>
<td>Not Determined</td>
</tr>
<tr>
<td>Challenge Dose</td>
<td>$10^6$ TCID$_{50}$ (i.t.)</td>
</tr>
<tr>
<td>URT protection</td>
<td>partial**</td>
</tr>
<tr>
<td>LRT protection</td>
<td>complete**</td>
</tr>
<tr>
<td>Species</td>
<td>Cynomolagus macaques</td>
</tr>
</tbody>
</table>
Safety Data

We first performed a single intramuscular injection experiment in Sprague-Dawley rats to evaluate the acute toxicity of EQUIVAX. Systemic anaphylaxis due to EQUIVAX was subsequently evaluated by intramuscular and intravenous injections in guinea pigs. The long-term toxicity of EQUIVAX was further evaluated in cynomolgus monkeys.
Summary

Initial studies demonstrate immunization with EQUIVAX promotes high levels of neutralizing antibody in six mammalian species, including rats, mice, guinea pigs, rabbits, cynomolgus monkeys, and rhesus macaques, protecting them against SARS-CoV-2 infection.

Study results demonstrated a two-dose immunization series using 2 mg/dose of EQUIVAX conferred highly efficient protection against SARS-CoV-2 in rhesus macaques without observable adverse effects or worsening immunopathological changes.
Target Product Profile
Elements of the TPP

# 1: Indications
# 2: Target population
# 3: Contraindications
# 4: Safety & Reactogenicity
# 5: Efficacy
# 6: Dose Regimen
# 7: Durability of Protection
# 8: Route of Administration
# 9: Coverage
# 10: Stability & Storage
# 11: Co-administration
# 12: Presentation
# 13: Production & Accessibility
# 14: Registration & Prequalification
# 15: Post Marketing Surveillance
# TPP#1: Indications

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic immunization protects against COVID-19 infection.</td>
<td>Immunization reduces the severity of COVID-19 disease</td>
</tr>
</tbody>
</table>
TPP#2: Target Population

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All individuals 1-year and older</td>
<td>Adults including the elderly</td>
</tr>
<tr>
<td>Preferred</td>
<td>Critical or Minimal</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
</tr>
</tbody>
</table>
| None      | ● Immunocompromised patients  
|           | ● History of severe allergic reaction to inactivated COVID-19 vaccine or known allergy to any of its components |
TPP#4: Safety & Reactogenicity

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, transient side effects</td>
<td>Safety and reactogenicity profile whereby vaccine benefits outweigh safety risks</td>
</tr>
<tr>
<td>No serious adverse effects</td>
<td></td>
</tr>
</tbody>
</table>
TPP#5: Efficacy

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• General Population: &gt; 70% efficacy</td>
<td>• General Population: &gt; 70% efficacy</td>
</tr>
<tr>
<td>• Older Adults*/Elderly: &gt; 70% efficacy</td>
<td>• Older Adults*/Elderly: &gt;55% efficacy</td>
</tr>
</tbody>
</table>

*older adults includes individuals age 65 and older
TPP#6: Dose Regimen

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose regimen (use of time released</td>
<td>Two dose regimen (administered 3-4 weeks apart)</td>
</tr>
<tr>
<td>injectable device acceptable)</td>
<td></td>
</tr>
</tbody>
</table>
TPP#7: Durability of Protection

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provides lifelong protection after single administration</td>
<td></td>
</tr>
<tr>
<td>• Booster dose not needed</td>
<td>• Confers protection for at least 12 months</td>
</tr>
<tr>
<td></td>
<td>• Annual boosters</td>
</tr>
</tbody>
</table>
## TPP#8: Route of Administration

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneous oral dose and parenteral administration of time released formulation</td>
<td>Any route of administration</td>
</tr>
</tbody>
</table>
## TPP#9: Coverage

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivalent</td>
<td>Monovalent</td>
</tr>
</tbody>
</table>
### TPP#10: Stability & Storage

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extreme Thermostability</strong></td>
<td><strong>Moderate Thermostability</strong></td>
</tr>
<tr>
<td>● Shelf life &gt; 24 months at -20 °C</td>
<td>● Shelf life &gt; 12 months at -20 °C</td>
</tr>
<tr>
<td>● Stability &gt; 12 months at 2-8°C</td>
<td>● Stability &gt; 1 month at 2-8°C</td>
</tr>
<tr>
<td>● Stability &gt; 12 months at 40-45°C</td>
<td>● Stability &gt; 12 months at 40-45°C</td>
</tr>
<tr>
<td>● Stability &gt; 2 years at 20-22°C</td>
<td>● Stability &gt; 8 hours at 20-22°C</td>
</tr>
</tbody>
</table>

Not light sensitive
TPP#11: Co-administration

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be given with other vaccines without affecting immunogenicity, safety or efficacy of the vaccines.</td>
<td>Must be used as a stand alone product</td>
</tr>
</tbody>
</table>
**TPP#12: Presentation**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Sterile liquid product for direct use</td>
<td>● Sterile liquid for direct use</td>
</tr>
<tr>
<td>● Single dose vial or prefilled AD syringe</td>
<td>or lyophilized product with simple reconstitution at point of use not requiring end-to-end cold chain</td>
</tr>
<tr>
<td>● Stored at room temperature, eliminating need for cold-chain requirement</td>
<td>● Single-dose or multi-dose presentation</td>
</tr>
</tbody>
</table>
### TPP#13: Production & Accessibility

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>● 9 billion doses or</td>
<td>● 350 million doses or</td>
</tr>
<tr>
<td>● Capability to rapidly scale up production (at cost/dose allowing for</td>
<td>● Availability of sufficient doses (at cost/dose) that allows for broad</td>
</tr>
<tr>
<td>broad use) in LMIC</td>
<td>use in LMIC</td>
</tr>
<tr>
<td>● Burden of cost to be covered collectively by upper &amp; middle income</td>
<td>● Burden of cost to be heavily</td>
</tr>
<tr>
<td>countries</td>
<td>subsidized by collective efforts of upper &amp; middle income countries</td>
</tr>
</tbody>
</table>
## TPP#14: Registration & Prequalification

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>● WHO prequalified</td>
<td>● Emergency Use Authorization (EUA)</td>
</tr>
<tr>
<td>● Meets criteria for Emergency Use Assessment &amp; Listing (EUAL) Procedure</td>
<td>● Expanded Access Program</td>
</tr>
</tbody>
</table>
## TPP#15: Post Marketing Surveillance

<table>
<thead>
<tr>
<th>Post Marketing Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Implementing local, reliable vaccine safety monitoring systems in remote areas at the time of vaccine administration</td>
</tr>
<tr>
<td>● Assessment of serious adverse effects</td>
</tr>
<tr>
<td>● Monitoring vaccine effectiveness</td>
</tr>
<tr>
<td>● Emergence of vaccine resistant SARS COV-2 mutants</td>
</tr>
</tbody>
</table>
Phase 3 trial details

- Population to be enrolled with inclusion and exclusion criteria
- Estimated duration of the trial
- Immunization schedule
- Primary outcome measure and how the outcome will be determined/measured
- Secondary outcome measures (up to 3) and how they will be determined/measured
- Briefly describe immunology studies and when samples will be collected
- Briefly describe how you will determine sample sizes for primary efficacy and safety outcomes
Phase 3 trial design
Overview and objectives

- Randomized, double-blinded, multinational trial conducted across low- and middle-income countries (LMICs)
- Enrollment of subjects from diverse socioeconomic backgrounds, collaborating with healthcare and community centers
- Enrollment of subjects with common underlying conditions
- Regular monitoring of symptoms, SARS-CoV-2 infection status, and additional outcome measures
- Regular monitoring of overall health status
Inclusion criteria

- Healthy subjects (age 18+)
- Female subjects of childbearing age who are not nursing/pregnant and have no family planning within first 3 months of enrollment
- Ability to understand study procedures, informed consent, and comply with study protocols
Exclusion criteria

- Confirmed/suspected SARS-CoV-2 infection
- History of SARS/MERS infection
- Associated symptoms within 14 days before vaccination (e.g. fever, dry cough, dyspnea, sore throat, diarrhea)
- Pregnancy or upcoming family planning within 3 months
- Previous severe allergic responses to vaccination or known ingredients
- Severe disease (e.g. uncontrollable hypertension, malignant tumors)
- Immunodeficiency (e.g. HIV, lymphoma, autoimmune diseases)
- Patients receiving immunotherapy
- Recent vaccinations (within 14 days, or 1 month for live-attenuated)
- Received other research drugs within 6 months
Duration and schedule

Duration

- 12 months after enrollment of last subject
- Allows effective monitoring of all subjects up to 12 months
- Weekly PCR testing, symptom check-ins, health check-ins after first dose up to 6 months
- Biweekly testing and check-ins up to 12 months

Schedule

- Two identical doses
- 21 days apart
Primary outcome measure

Incidence of COVID-19 cases after two doses of vaccination

- Comparison of COVID-19 case numbers between intervention and placebo arms
- Between 14 days and 12 months after 2nd dose
- PCR tests being administered every week, performed at a central laboratory in a blinded fashion
Secondary outcome measures

Severe COVID-19 cases and deaths

- Monitoring for severe cases and deaths due to COVID-19
- Between 14 days and 12 months after 2nd dose

Incidence of short-term adverse events (AEs)

- Monitoring subjects through self-reporting
- Up to 12 months after each dose
Secondary outcome measures

Incidence of long-term serious adverse events (SAEs)

- Monitoring subjects through self-reporting
- Up to 12 months after each dose

Antibody levels against SARS-CoV-19

- Blood samples for serum antibody analysis (*immunological studies*)
- Various time points after vaccination course
Immunological studies

Geometric mean titer (GMT) of anti-SARS-CoV-2 antibodies
- Geometric mean of antibody titer

Geometric mean fold rise (GMFR) of anti-SARS-CoV-2 antibodies
- Geometric mean of ratio of post-vaccination titer to pre-vaccination titer

Four-fold increase rate of anti-SARS-CoV-2 antibodies
- Rate of four-fold increase in titer (seroconversion)

Time points: 14 days, 28 days, 3 months, 6 months, 9 months, 12 months after 2nd dose
Sample size

- Our sample size is based on our
  - Desired power (80%)
  - Desired confidence (95%)
  - 1:1 vaccine : placebo allocation
- Our target sample size for Phase 3 is 30,000 participants
- Increasing sample size allows us to have a representative and replicative trial
Phase 4 trial

- Phase 4 will begin after the drug is approved
- Phase 4 will including continuous surveillance and measuring different outcomes of interest
- Looking at vaccine outcomes in populations of interest that were not included in phase 3 clinical trials
Phase 4 trial: Outcomes of interest

- Long-term side effects and adverse events
- Long-term vaccine efficacy
- Long-term vaccine safety
- Monitoring of severe adverse effects
- Effectiveness against different strains
Vaccine distribution in LMICs

- Healthcare workers at risk of being exposed to COVID-19
- People over 75 years of age
- Other frontline/essential workers (e.g. law enforcement, firefighters, public transit workers)
- People over 65
- People under 65 with 2 or more comorbidities
Current status

- Ongoing phase 3 trials conducted for the Sinopharm vaccine in Bahrain, Egypt, Jordan, UAE, Peru, Argentina, etc.
- Approved and being used in China, UAE, Bahrain, Peru, Jordan, etc., among other countries in Europe, Africa, South America, Asia

- UAE government reports 86% efficacy
- Chinese government reports 79.34% efficacy
Current status

With the tailoring of our Phase 3 and 4 trials geared toward LMICs, we strive to fulfill our mission to play our part in fighting the global pandemic by vaccinating both with efficacy and equity.
Sources

- https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189890/
- https://clinicaltrials.gov/ct2/show/NCT04510207
- https://covid19.trackvaccines.org/vaccines/5/
- https://www.who.int/biologicals/expert_committee/Clinical_changes_IK_final.pdf
- https://clinicaltrials.gov/ct2/show/NCT04612972
- https://clinicaltrials.gov/ct2/show/NCT04560881