COVI-VAC, Single-dose, Intranasal Live Attenuated Vaccine Against SARS-CoV-2:

- ✓ 2nd generation Covid-19 vaccine
- ✓ Live-attenuated full virus vaccine
- ✓ Broad immune response
- ✓ Potential to protect to variants
- ✓ Intranasal administration
- ✓ Single dose regimen
- ✓ In human clinical studies in UK
- ✓ Demonstrated efficacy & safety
- ✓ Suitable for mass vaccination
- ✓ Upscaling of manufacturing in NL

Partnership

- The COVI-VAC vaccine is based on Codagenix' breakthrough technology for live-attenuated virus design.
- Codagenix and Serum Institute of India Private Limited ("SIIPL") entered into a collaboration to rapidly co-develop COVI-VAC.
- Bilthoven Biologicals ("BBIO") is worldwide leading manufacturer of polio vaccines with extensive expertise of Verocell- and microcarrier-technology.
- After successful preclinical studies with COVI-VAC, a Phase I study started in December 2020 in the UK (enrollment completed).

Development Plan

- Given the ongoing spread of Covid-19 worldwide and likelihood of mutations, it is critical to expedite the development of COVI-VAC, the only single-dose, intranasal live attenuated vaccine.
- The Netherlands could play a vital role in expediting the development of COVI-VAC:
  1. Within NL there is an excellent clinical trial network, with UMCU as one of the key clinical trial centers.
  2. BBIO could free-up facilities for upscaling the manufacturing of COVI-VAC based on Verocell-microcarrier technology and/or manufacture at risk
  3. There are various potential vaccine development partners in NL, which could expedite process development for large scale COVI-VAC manufacturing
- By entering into a cooperation agreement at this stage of the development process, the Dutch government has the opportunity to secure timely access to COVI-VAC.
- The Netherlands could extend its heritage in making effective and affordable vaccines available to Europe and the world.

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Live-attenuated vaccine

- Live attenuated viral vaccines are known to be most effective in inducing a robust, broadly protective immune response:
  1. Antigen presentation that mimic natural infection,
  2. Induction of immunity against both the structural and non-structural proteins
  3. Induction of both the humoral and cellular immune response
  4. Broader immune response to drifted strains.
- Historically, generation of live attenuated virus strain is a laborious and at times a random process with limited knowledge of the mutations leading to attenuation.
- Most of Covid-19 vaccines focus on the spike protein, whereas COVI-VAC is based on the whole virus in attenuated form.

COVI-VAC attenuated vaccine design

- The COVI-VAC vaccine is based on a breakthrough approach to live-attenuated virus design wherein the viral genomes is processed in a computer-based algorithm to introduce hundreds of silent mutations into the genome to use codon pairs that are underrepresented in human cells.
- The resulting genome translates proteins identical at the amino acid level with the wild type virus, yet "de-optimized" for translation efficiency in the human host cell.
- COVI-VAC, a live attenuated vaccine for prevention of COVID-19 was developed using the "Synthetic Attenuated Virus Engineering" (SAVE) platform to recover rationally designed, deoptimized candidate (CDX-005) from the wild type coronavirus strain 2019-nCoV/USA-WA1/2020 (WA1).
- The result is a genetically stable, rationally-designed, live vaccine:

  COVI-VAC carries 283 silent mutations and a deletion of the furin cleavage site in Spike

COVI-VAC – Development Plan NL

Live attenuated vaccine against COVID-19

Preclinical results

- Safety and immunogenicity of the vaccine technology is shown in multiple models:
  - ✓ Seasonal influenza (phase I)
  - ✓ RSV (primates)
  - ✓ Dengue (primates)
- For the COVI-VAC vaccine no mutation detected in the de-optimized region or the furin deletion site after 20 passage from working seed in Vero cells.
- COVI-VAC is stable at -20°C, with 4°C formulation in development
- COVI-VAC demonstrated safety & efficacy against wild-type challenge in hamsters and non-human primates after one dose, only 14 days post-vaccination
- In hamsters, COVI-VAC elicited a higher titer of neutralizing antibodies than infection with wildtype virus.
- COVI-VAC elicited better cross-neutralization against B.1.351, South-African variant, than con-valescent sera.
- Preclinical results give further base for the robust immune response to be expected from live-attenuated vaccines.

Clinical Phase I trial in UK

- Randomized, double-blind, placebo-controlled, dose-escalation trial.
- 48 volunteers to be evaluated at three dose levels.
- Design is based on 3 dose escalating cohorts.
- Endpoints include safety, tolerability and immunogenicity.
- Dosing of first patient started in January 2021.
- As of April 2021, the study is fully enrolled, report of initial data expected by mid-2021.
- Pending results of the Phase 1 trial, planning of further clinical studies is starting now (see next page).

COVI-VAC – Development Plan NL

Live attenuated vaccine against COVID-19

Regulatory and Clinical Plans

- Until now, the regulatory and clinical plans for COVI-VAC are **outside EU**:
  - Extensive conversations with FDA ongoing, real-time
  - Phase 1 study ongoing in the UK
  - Phase 1b/2 dose confirming study for Q3 2021 in Latin America
  - Pediatric Phase 1/2 trial also planned for Q3 2021 in US
  - Phase 2/3 active comparator study planned to start Q3 2021 in Asia
- Proposal to Dutch government is to discuss the options how to expedite development and getting Netherlands and EU involved.

Proposal to Dutch government

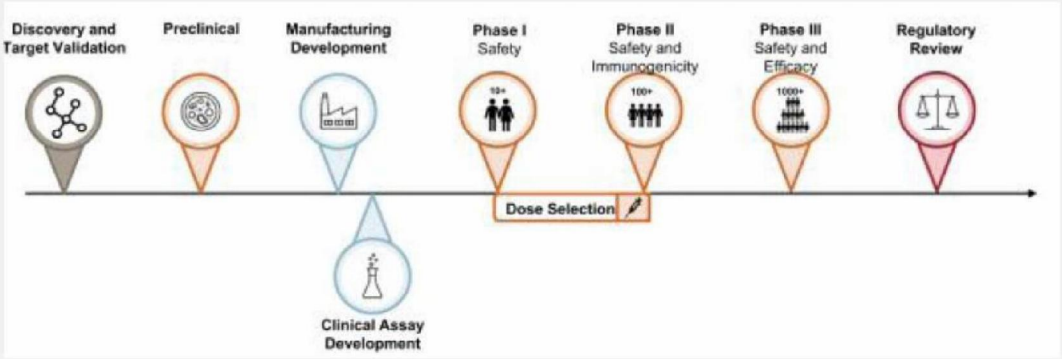
The development of COVI-VAC could be expedited with financial support of the Netherlands. The following steps could be taken:

1. Design and preparation of phase 3 study in NL **(Q2-Q3 2021)**
2. Executing clinical trial phase 3 in the NL **(Q4 2021 onwards)**
3. Process development for large-scale manufacturing at BBIO **(Q2-Q3 2021)**
4. Free-up manufacturing capacity at BBIO for tech transfer, engineering and validation batches **(Q4 2021 onwards)**
5. Manufacturing of COVI-VAC at risk by BBIO **(2022 onwards)**

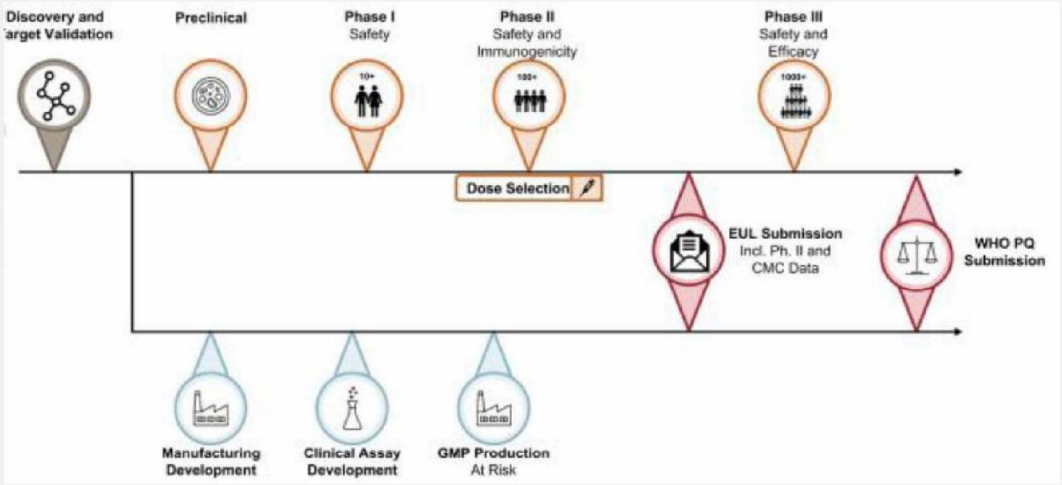
- The funding requirement is depending on multiple factors including size of clinical trial and manufacturing volumes.
- Estimated required funding for step 1 until 4 is in the order of **EUR** 5.1.1c subject to further detailing of development plan.
- A cooperation agreement may consist of upfront payments, milestone-based payments and/or advanced purchase agreement.

Development Plan

The traditional development pathway for vaccines:



With support from the Dutch government the development could be accelerated for COVI-VAC:



Figures: Potential for acceleration across all aspects of development for an EUL submission, Nature 22 April 2021

Key to the acceleration of COVI-VAC development is the combination of:

- Early preparation and execution phase 3 clinical trial in The Netherlands and
- Development of manufacturing process at Verocell-microcarrier technology in parallel.

Dutch vaccine initiative

- This Dutch public-private initiative strengthens the vaccine value chain in NL bridging clinical development towards vaccine manufacturing.
- BBIO and UMCU are key stakeholders for this Dutch initiative, which may be extended with further Dutch vaccine partners.
- This initiative is supporting the EU strategy to increase and strengthen vaccine manufacturing on European soil.
- COVI-VAC is anticipated to have a broad immune response with single-dose administration, which fits the EU (booster) vaccination program post-2021.
- The upscaling of vaccine manufacturing based on Vero-cell technology of BBIO does increase worldwide availability of COVI-VAC at affordable prices.
- COVI-VAC has the potential to address several key logistical challenges to immunization at a global scale.
- From all these perspectives, Dutch government can have a substantial impact on global health.

Next steps

- Parties are highly interest to explore further cooperation with the Dutch government, on due course, to explore the feasibility of this initiative.
- Given the urgency of the matter, parties are available at your request for further exploring this initiative.
- Primary contact points for Dutch government with respect to this initiative are:

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