



## EU Commission – COVID-19 vaccine meeting agenda

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1. Vaccine development status
2. Plans for clinical trials (and indicative timelines)
3. Current production capacity: scale, location – potential number of doses / regimens available for the EU (and also for the rest of the world)
4. Support from EU commission and impact on timelines and production scale
5. Type of agreement
  - Upfront support to vaccine development and production capacity
  - Advance purchase agreements (APAs)

## COMPANY PROFILE

- ReiThera is an **Italian biopharmaceutical SME** with research labs in Rome and Naples and a GMP Manufacturing Facility and Headquarter in Castel Romano (Rome)
- ReiThera has 80 employees



6,000 SQM FACILITY DEDICATED TO THE DEVELOPMENT AND APPLICATION OF INNOVATIVE VIRAL VECTORED PLATFORM TECHNOLOGIES

<https://www.reither.com>

**Our mission** is to develop innovative viral vectored platform technologies for infectious diseases and advanced therapies

## REITHERA'S ORGANIZATION & CAPABILITIES

**ReiThera's team** has strong expertise in the development and manufacture of vaccines based on viral vectors starting from wild-type strains and transgene engineering to GMP BDS/DP production.



The team can support clinical translation of internal and external projects offering regulatory and clinical operation capabilities.



### Research Labs

Immunology Unit  
Vectorology Unit  
Antibody Technology Unit



### PD Labs

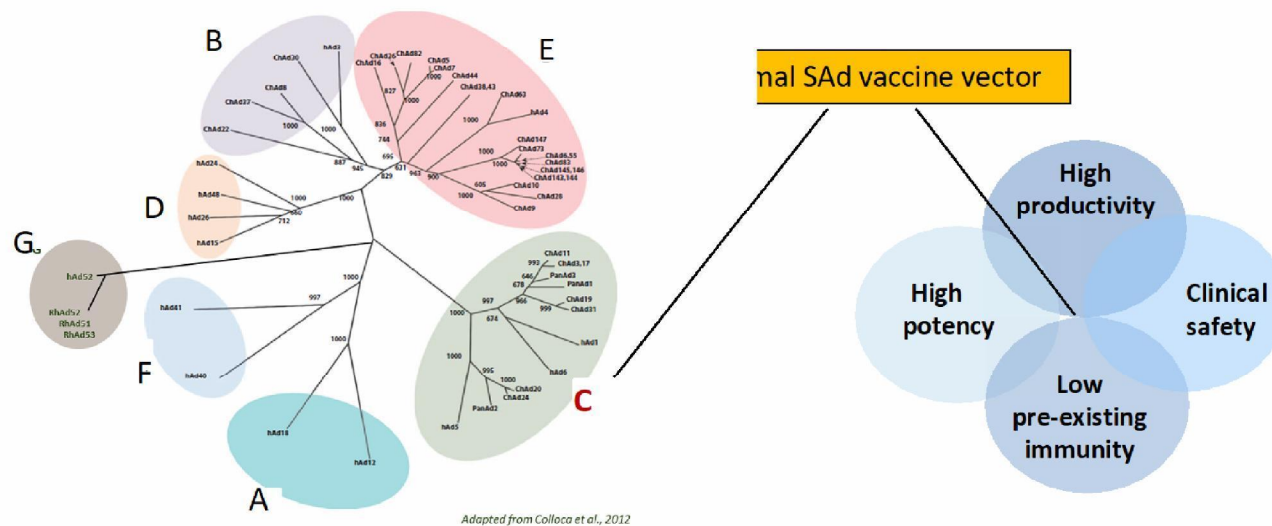
Upstream Unit (cell engineering & process scalability)  
Downstream Unit (advanced purification technologies)



### State of the Art GMP Facility & QC labs

Assay qualification/validation Unit  
QA Unit  
GMP production and release Unit

Some of these isolates have been successfully exploited for vaccines against major infectious diseases, including Respiratory Syncytial Virus, malaria, HIV, and Ebola.



- Leveraging on extensive experience, ReiThera has identified the **relevant attributes for a successful SAd-vectored vaccine platform**

## REITHERA HAS DEVELOPED A PROPRIETARY VACCINE PLATFORM TECHNOLOGY BASED ON A NOVEL GORILLA ADENOVECTOR

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### GRAd VECTOR

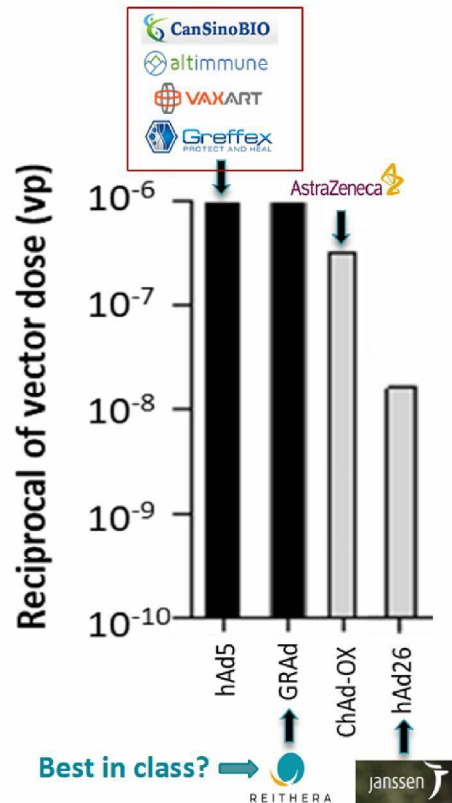
- Novel **group C** adenovirus strain isolated from stools of a captive healthy gorilla
- Related to several clinically validated simian Ad vector
- Low seroprevalence on human sera with respect to hAd5 and other ChAd vectors
- Strong immunological potency (humoral & cellular immune responses in mice)



### ReiCell35S PRODUCTION CELL LINE

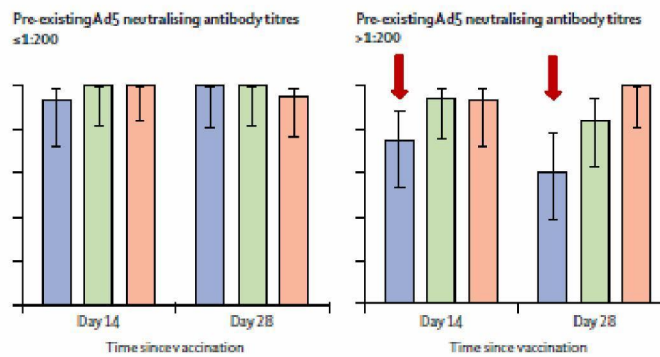
- Suspension-adapted packaging/production cell line derived from low passage (p6) HEK-293 cells
- Detailed history starting from 70's HEK 293 original record
- Silencing of transgene expression
- High productivity and low frequency of vector genomic instability

## A CROWDED SCENARIO OF COVID-19 ADENO-VECTORED VACCINES



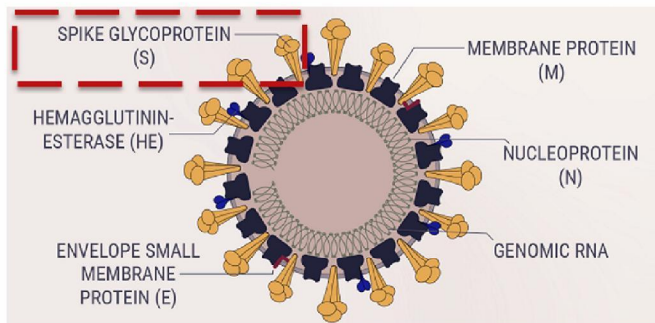
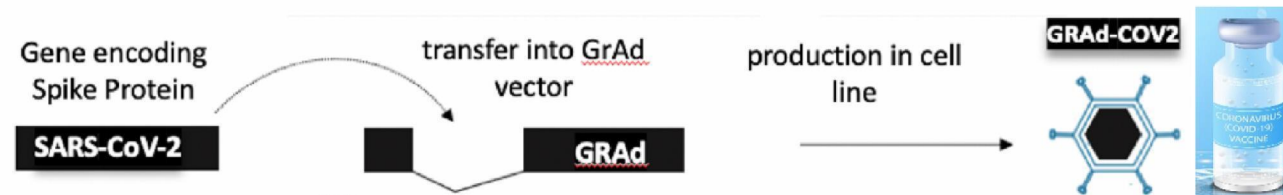
Results of Cansino Phase I trial of Ad5-SARS-CoV-2 showed that Ad5 pre-existing immunity >200:

- slowed down and lowered the peak of immune responses, particularly for humoral immunity
- might have a negative effect on the persistence of vaccine-elicited immune responses

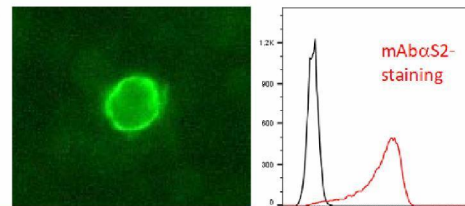


Zhou et al The Lancet, May 2020

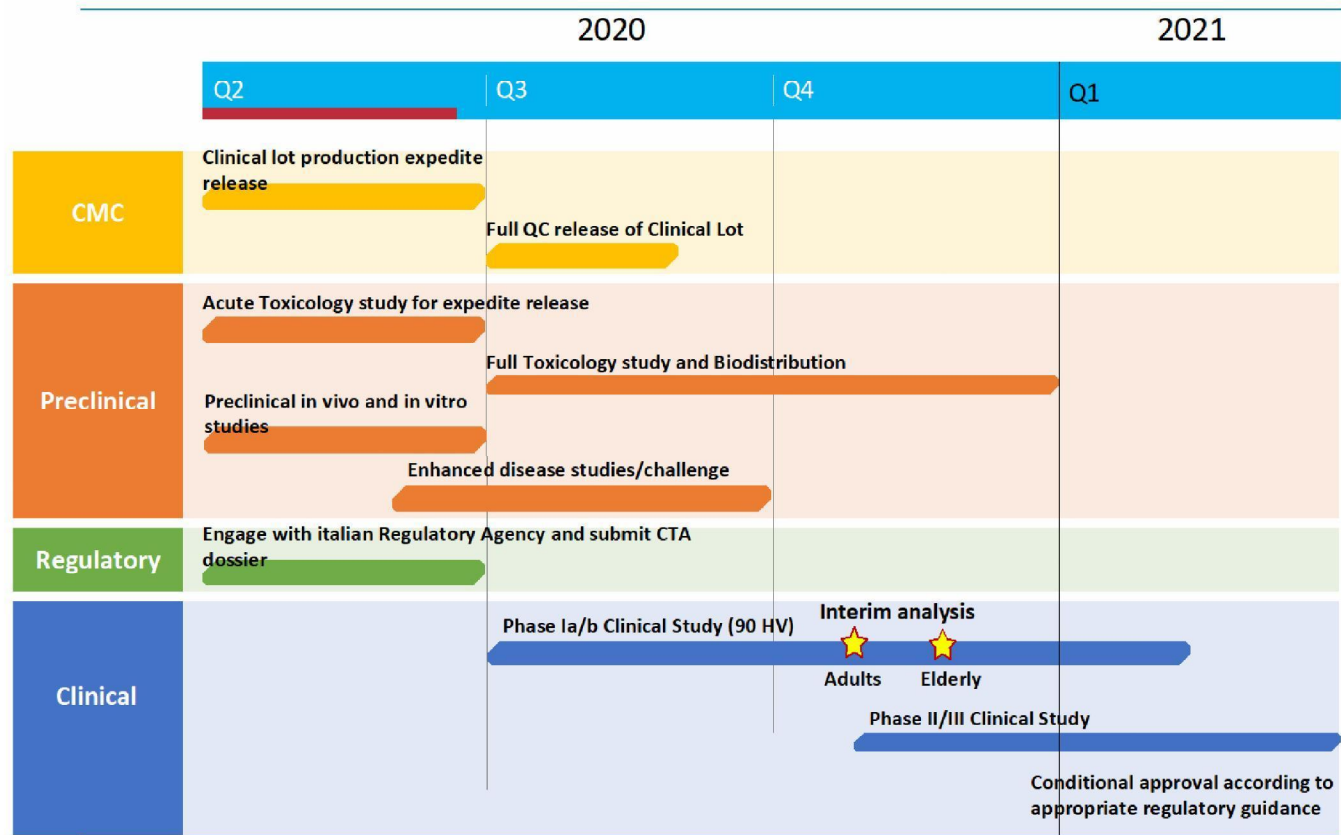
## REITHERA'S VACCINE for COVID-19: GRAd-COV2



- ✓ The vaccine antigen is the **prefusion stabilized full length Spike protein\*** (K986P, V987P)
- ✓ Upon infection of cells with GRAd-COV2 the Spike protein is correctly displayed on the cell membrane



## RAPID DEVELOPMENT OF GRAd-COV2 VACCINE – PLANS & STATUS as of June 2020



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# PRECLINICAL DATA

## GRAd-COV2 IMMUNIZATION IN MICE – SUMMARY OF PRECLINICAL DATA

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### Vaccination protocol and immunological assay:

- \* BALB/c mice immunized by a single intramuscular injection- two doses:  $10^8$  and  $10^9$  vp GRAd-COV2
- \* T-cell and humoral responses were evaluated in individual mice by:
  - Elispot and FACS analysis with 2 pools of overlapping 15mer peptides encompassing the SARS-Cov-2 Spike aminoacidic sequence: pool S1 and S2 (158 and 157 peptides each respectively, JPT PepMix)
  - Evaluating spike IgG titers at 2 and 5 wks post-immunization and neutralizing titers at 5 wks post-immunization by SARS-CoV-2 (2019-nCoV/Italy-INMI) microneutralization assay on VERO E6 cells and by neutralization assay with SARS-CoV-2 Spike HIV pseudotypes

### Results:

#### T-cell response

- \* IFN $\gamma$  ELISpot on splenocytes, total Spike (S1+S2) and individual pools corrected of DMSO background showed strong, **>1000 SFC / $10^6$  splenocytes** with  $10^8$  vp/dose and **>1500 SFC / $10^6$  splenocytes** with  $10^9$  vp/dose
- \* Both CD4 and CD8 were measured by IFN $\gamma$ , IL2 intracellular staining and FACS analysis

#### Humoral response

- \* SARS-CoV-2 (2019-nCoV/Italy-INMI) microneutralization assay on VERO E6 cells with serum from mice immunized with both  $10^8$  and  $10^9$  vp/dose showed neut titers comparable to what measured in convalescent patients

## IN RHESUS MACAQUES IN COLLABORATION WITH VRC/NIH

### Animals:

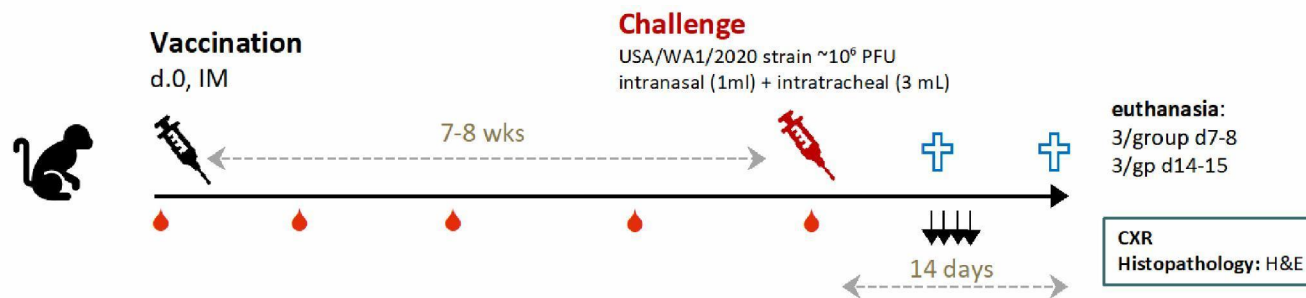
- Rhesus macaques
- 4-8 years old
- 6/group, 18 total

### Vaccines Groups:

- |                      |                      |
|----------------------|----------------------|
| A: GrAd-COV2         | $1 \times 10^{11}$   |
| B: GrAd-COV2         | $2.5 \times 10^{10}$ |
| C: GrAd32 (unrel Ag) | $1 \times 10^{11}$   |

### Time points:

- |                |                   |
|----------------|-------------------|
| ▪ Vaccination: | Jun. 11           |
| ▪ Challenge:   | July 27 or Aug. 3 |
| ▪ Euth./histo: | Aug. 10 onwards   |



### Immunogenicity

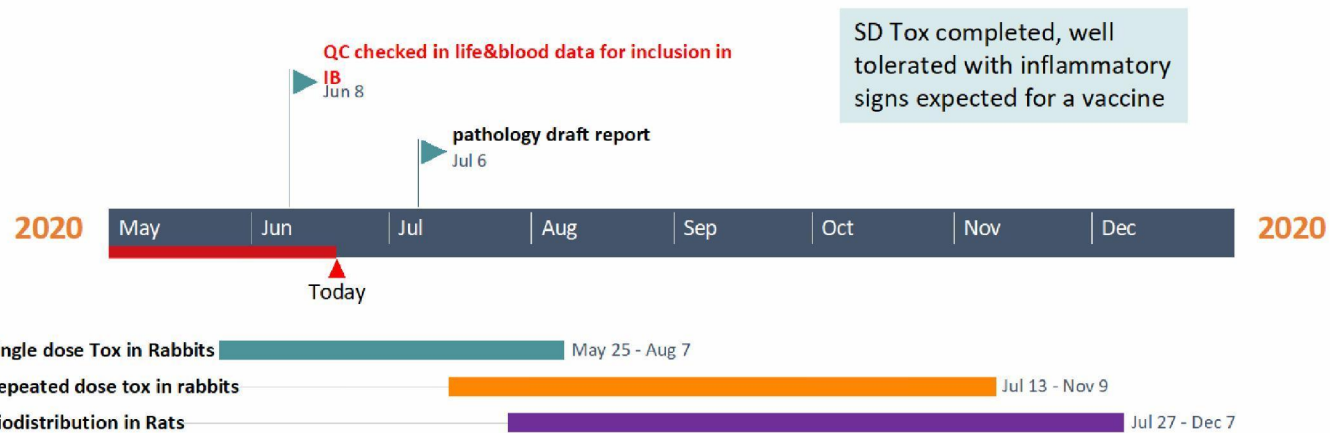
- Serology: Spike Ab titers in plasma and BAL, Neutralizing Abs, RBD/ACE2 block, System serology
- Transcriptional signature (whole blood and single cell analysis of SPIKE specific T and B cells)
- Cellular immunity (PBMC/BAL): Th1/Th2/Th17/TfH ICS 19-color, S1/S2/N peptides

### Viral replication: post-challenge

- PCR subgenomic, PFU- nasal swabs and BAL
- Pathology
- Viral Load-Lung tissue

## TOXICOLOGY ROADMAP

- \* Roadmap pre-agreed with Italian regulatory agency
- \* Phase I trial enabled by a single dose tox study in Rabbits to exclude acute toxicities
- \* Repeated dose tox in Rabbits & biodistribution in Rats run in parallel with phase I trial



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# CLINICAL DEVELOPMENT PLAN

## GRAd-COV2 VACCINE Phase I CLINICAL STUDY - I

A phase I, dose-escalation study to assess the safety and immunogenicity of COVID-19 vaccine GRAd-COV2 in healthy adults and elderly subjects

Study code: RT-CoV-2

### Study design

| Arms | N° of Adults & Elderly |    | Treatment | Dosage                | Route | N° of dose | Description of Study Group |
|------|------------------------|----|-----------|-----------------------|-------|------------|----------------------------|
| 1    | 15                     | 15 | GRAd-COV2 | 5x10 <sup>10</sup> vp | IM    | 1          | Low dosage                 |
| 2    | 15                     | 15 | GRAd-COV2 | 1x10 <sup>11</sup> vp | IM    | 1          | Middle dosage              |
| 3    | 15                     | 15 | GRAd-COV2 | 2x10 <sup>11</sup> vp | IM    | 1          | High dosage                |

Estimated enrollment: 90 volunteers (45 aged 18-55y and 45 aged 65-80y)

Clinical Trial leadership: INMI-Spallanzani, Rome, Italy

Sponsor: ReiThera Srl

Clinical sites: INMI-Spallanzani (Rome), CRC Phase (Verona), ITALY

## GRAd-COV2 VACCINE Phase I CLINICAL STUDY - II

**Primary objective:** overall safety and reactogenicity

**Secondary objective:** assessment of cellular and humoral immune response elicited by the vaccine at 2, 4, 8, 12 and 24 weeks. This includes:

- antibodies to SARS-CoV-2 Spike protein (anti-S-Ab)
- antibodies to SARS-CoV-2 nucleocapsid (anti-N-Ab)
- SARS-CoV-2 micro-neutralization assay to quantify neutralizing antibody activity to the virus
- Ex vivo IFN- $\gamma$  ELISpot responses to SARS-CoV-2 Spike protein

**Exploratory (tertiary) objectives:** in depth characterization of humoral and cellular response to vaccination

### Estimated timeline



## GRAd-COV2 VACCINE Phase IIb/III CLINICAL STUDY – Assumptions

A Randomized, Double-blinded, Placebo-controlled, multicentered Phase IIb/III Clinical Trial to Evaluate Safety, Immunogenicity and Efficacy of COVID-19 vaccine GRAd-COV2

| Group | Treatment                              |
|-------|----------------------------------------|
| 1     | GRAd-COV2 – dose selected from Phase I |
| 2     | Placebo                                |

### Assumptions:

- Multi-country submission, then adapt the numbers to real time local epidemic
- Incidence of symptomatic disease might be too low; need to use a serology endpoint
- We may be able to use a serological correlate of immunity if data from an adenoviral vectored vaccine will be available

If not, then: assume ongoing 2% infection rate by serology, 0.6% by PCR

Assume 80% vaccine efficacy (VE)

Assume 6 month follow up

### Trial size:

Based on serological conversion over six months would be about

3000 for 2% incidence and 80% efficacy

6000 if incidence drops to 1%; up to 12,000 if efficacy is 60%

### Timeline:

Scientific advice & protocol development: July – Oct 2020; CTA filing: Nov 2020; start Nov/Dec 2020

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## PRODUCTION CAPACITY: PRESENT & NEAR FUTURE

## GRAd-COV2 PRODUCTION PROCESS

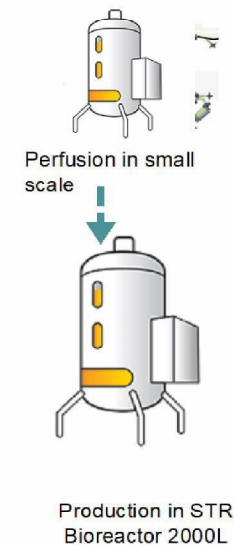
### Upstream process

- ReiCell35S cell adapted to suspension growth
- Cell expansion in stirred tank bioreactor under perfusion
- Production in single use stirred tank bioreactor
- Harvesting 72 hrs post-infection

### Downstream process

- Cell lysis in bioreactor bag by detergent
- HC-DNA precipitation
- Depth filtration
- Membrane chromatography
- Polishing step by mixed mode chromatography
- DNA trimming step by nuclease digestion
- Formulation by TFF

- The entire process is based on single use technologies – easy scale up and tech transfer to other facilities



## CLINICAL LOT PRODUCTION ON 200L SCALE USING REITHERA STANDARD PROCESS

- Clinical lot production in 200L STR (Cell density: 5E5 cell/ml)
- Downstream process steps based on chromatography and TFF
- Yield = 1 dose/ml of bulk – Dose=1E11 vp
- Very low levels of process residuals
- >60% yield in the downstream process

| Process step                     | Total vp | Volume | hcDNA ng/mL | Doses          |
|----------------------------------|----------|--------|-------------|----------------|
| Bulk                             | 2,00E+16 | 190000 | ND          | <b>200.000</b> |
| Post-clarification               | 1,73E+16 | 211000 | 7214        | <b>173.000</b> |
| Membrane chromatography          | 1,65E+16 | 263000 | 46,5        | <b>165.000</b> |
| Polishing and nuclease digestion | 1,21E+16 | 7100   | <LOD        | <b>121.000</b> |
| Formulated Drug Substance        | 1,23E+16 | 7100   | <LOD        | <b>123.000</b> |

**Process intensification ongoing directed to higher volumetric productivity**

## GRAd-COV2 VACCINE PRODUCTION ON LARGE SCALE – PLAN FOR DS PRODUCTION

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- \* Vaccine manufacturing capacity expansion – 600 additional sqm
  - o Process scale up from 200L to 3000L in STR starting from Sept 2020
  - o Production target: 5 million doses per run – 4 runs per month
  - o **>200 million doses per year from 4Q-20 including fill-finish**
  
- \* Process intensification ongoing by:
  - o Implementation of perfusion in the production process
  - o Increasing cell density at infection
  - o Increasing volumetric productivity – initial target= 3 doses/ml
  - o Refining/simplifying downstream process– cost reduction
  - o High cell density/high volume WCB production in bags
  - o Large scale working seed production

Capex = 20 million €  
Opex = 3€ /dose

## GRAd-COV2 VACCINE PRODUCTION ON LARGE SCALE – PLAN FOR DP PRODUCTION

- \* Drug Product manufacturing is a bottleneck in large-scale manufacturing

### Single-dose vials

- Easy to use and to keep sterile, familiar to end users and regulators
- Limited capacity, high costs, glass shortage

### Multidose vials

- Increased capacity (10-20x), reduced costs, lower volume in storage and shipment
- Might require preservative which impacts stability

- MEDInstill solution

- 200-dose bag made from multilayer film, with ports for filling and for dispensing
- Sterility is maintained during both filling and dispensing
- Large increase in filling capacity, low environmental requirements for filling and dispensing, reduced costs, reduced volume for storage and shipment



Intact Luer bag

- Reithera is planning to install MedInstill filler by October to be able to fill 31000 bags (= 6.2 million doses) per day (3 shifts)
- Exceeding filling capacity can be offered to other vaccine manufacturers

## GRAD COV2 VACCINE DEVELOPMENT

### EUROPEAN CONSORTIUM FOR EFFICIENT SCALING UP & FORMULATION

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- **Strategic collaboration with the goal to:**
  - accelerate the development of a thermostable formulation
  - scale up production to million doses



- Improved proprietary formulation already available
- Tested on different Ad serotypes
- Adaptation to GRAd vector ongoing



- Owner of an innovative technology based on fixed bed bioreactors
- Capability for large scale production of viral vectors >2 million doses/run

➤ **Production process can be transferred to additional vaccine manufacturers worldwide**

## ReiThera business model: working as CDMO for third parties

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### CDMO model

- Expertise on production of biologics based on upstream process using mammalian or insect cells and downstream process based on chromatography and TFF
- ReiThera is currently offering the internal expertise to third parties. Partnership with Sabin Vaccine Institute and BARDA for the development of Ebola and Marburg vaccines
- Excess of DS production capacity can be offered for the manufacture of other vaccine if GRAd-COV-2 is unsuccessful
- Excess of DP production capacity in Intact multidose bags can be offered externally in parallel with GRAd-COV2 vaccine production

## Potential support from EU commission

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### **Support from EU with the goal to:**

- accelerate the development of the vaccine up to authorization
- scale up production to million doses

### **Vaccine development costs**

- Assume 3,000 person study
- CRO costs about 13-16M euros

### **Costs: Overall 25M**

### **Production scale up milestones and costs**

- Expansion of the current capacity from 200L to 3000L (200 MLN doses/year)
- Intensification of DP production process by MedInstill filler
- Collaboration with Univercells to duplicate production capacity and to transfer production process to additional manufacturers

### **Timeline: to be ready by November 2020**

**Costs: 20 MLN € CAPEX plus Opex (approx 3€/dose)**

**ReiThera is willing to negotiate APA to provide equitable access to the GRAd COV-2 vaccine**

## BACK UP

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## OUR HISTORY

### Okairos mission:

development of innovative vaccines for infectious diseases based on the chimp-adenovector platform

### ReiThera mission:

development of innovative viral vectored platform technologies for infectious disease and advanced therapies

