Table 9: List of Studies

Study ID (Status) Phase	Study Population	Region/ country [number of sites]	Primary Objective(s)	Sample size	Groups (ratio)	Study Start/ Duration	Laboratory Read-outs (Number of subjects, TimePoints)	Design (number of visits)
CV-NCOV-001 (Ongoing) Phase 1 (FIH)	Healthy adults (18-60 years)	Europe (Germany, Belgium) [4]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels	≥168	1) Open-label sentinel group 2) 2 groups within each dose level (4.5:1) • CVnCoV • Placebo	June 2020/ 13 months	• ELISA Spike IgM and IgG (all, 10 TP) • SARS-CoV-2 neutralising activity (all, 10 TP) • ELISA N-antigen IgG (all, 10 TP) • Cytokines (12 per dose level) • Gene expression profiling (12 per dose level) • CMI (≥12 per dose level) • serology assessments (12 per dose level) • PCR	partially blind, placebo-controlled, dose escalation (10-12)
CV-NCOV-002 (Planned) Phase 2a	Healthy subjects including older adults (≥61 years and 18-60 years)	Latin America (Panama, Peru) [2]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels • humoral immune response after 1 and 2 dose administrations of CVnCoV at different dose levels	700	Initial phase (10:1 within an age group): • 3 CVnCoV groups vs • 2 control vaccine groups + (1 non-randomised CVnCoV group) Expansion phase: 2 groups per age group (10:1) • CVnCoV • Control vaccine	Aug-Sept 2020/ 13 months	• ELISA Spike IgM and IgG (all, 6 TP) • ELISA N-antigen IgG (all, 6 TP) • Virus neutralisation (~251, 6 TP) • Cytokines (~100, 2 TP) • CMI (~100, 4 TP) • PCR	partially blind, controlled, dose confirmation (6-7)

Study ID (Status) Phase	Study Population	Region/ country [number of sites]	Primary Objective(s)	Sample size	Groups (ratio)	Study Start/ Duration	Laboratory Read-outs (Number of subjects, TimePoints)	Design (number of visits)
Efficacy Studies								
CV-NCOV-004 (Planned) Phase 2b/3 (pivotal)	Healthy subjects (≥18 years)	Asian, Europe, Latin America Other regions TBC# [~30]	• efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 disease • safety of CVnCoV administered as a 2-dose schedule to adults 18 YOA or older	19000	2 groups (1:1) • CVnCoV • Control vaccine	Nov 2020/ UNK*	• ELISA Spike IgG (1600, 6 TP) • Virus neutralisation (100, 3 TP) • ELISA N-antigen IgG (all, 2 TP + 200, 4 additional TP)	run-in Phase 2b + large Phase 3: randomised, observer-blinded, controlled (3, 6 or 7)
CV-NCOV-005 (Planned) Phase 2b/3	Healthy subjects (≥18 years; HCW)	Mainz (Germany) [1]	• safety and reactogenicity of CVnCoV administered as a 2-dose schedule to adults 18 YOA or older • antibody responses to the spike (S) protein of SARS-CoV-2 after 1 and 2 doses of CVnCoV	2500	2 groups (4:1) • CVnCoV • Control vaccine	Nov 2020/ UNK*	• ELISA Spike IgG (all, 6 TP) • ELISA N-antigen IgG (all, 2 TP) • Virus neutralisation (250, 3 TP) • PCR	randomised, observer-blinded, controlled (6)
Non-interventional Studies								
COVID19-5-P-002** (Planned) n/a	Adult, HCW	Mainz (Germany) [1]	• measurement of SARS-CoV-2 specific antibodies in a cohort of hospital employees in order to obtain the rate of seroconversion due to SARS-CoV-2 infections • prevalence of virologically-confirmed COVID-19 disease in a cohort of hospital employees, according to the FDA case definition of virologically-confirmed symptomatic COVID-19 clinical disease	3500	n/a	Aug 2020/ 6 months	n/a	prospective observational cohort study (4)
Special Populations								

Study ID (Status) Phase	Study Population	Region/ country [number of sites]	Primary Objective(s)	Sample size	Groups (ratio)	Study Start/ Duration	Laboratory Read-outs (Number of subjects, TimePoints)	Design (number of visits)
CV-NCOV-003 (Planned) Phase 2b	Adults with co-morbidities	Europe (Belgium, Germany) [8]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV • humoral immune response after 1 and 2 dose administrations of CVnCoV	1200	2 groups (1:1) • CVnCoV • Placebo	Nov 2020/ UNK*	• ELISA Spike IgG (all, 6 TP) • ELISA N-antigen IgG (all, 2 TP) • Virus neutralisation (180, 3 TP) • PCR	Placebo controlled (6)
CV-NCOV-006 (Planned) Phase 3	IC patients (HIV-infected adults)	Uganda or Mozam-bique [4]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV • humoral immune response after 1 and 2 dose administrations of CVnCoV	250	2 groups (1:1 TBC) • CVnCoV • Control vaccine	1Q21/ UNK*	• ELISA Spike IgG (all, 6 TP) • ELISA N-antigen IgG (all, 2 TP) • Virus neutralisation (100, 3 TP) • PCR	controlled if no efficacy data are available at study start (6)
CV-NCOV-007 (Planned) Phase 3	Pregnant women	Europe (4-5 countries, TBC) [10]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV • in their offspring: safety of CVnCoV administered as a 2-dose vaccine to the mother • humoral immune response after 1 and 2 dose administrations of CVnCoV	300	2 groups (1:1) • CVnCoV • Control vaccine	1Q21/ UNK*	• ELISA Spike IgG (all, 6 TP) • ELISA N-antigen IgG (all, 2 TP) • Virus neutralisation (100, 3 TP) • PCR	Controlled (8)
CV-NCOV-008 (Planned) Phase 3	IC patients (adults with malignancies)	Europe (4 countries) [8]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV • humoral immune response after 1 and 2 dose administrations of CVnCoV	250	2 groups (1:1 TBC) • CVnCoV • Control vaccine	1Q21/ UNK*	• ELISA Spike IgG (all, 6 TP) • ELISA N-antigen IgG (all, 2 TP) • Virus neutralisation (100, 3 TP) • PCR	controlled if no efficacy data are available at study start (6)
Paediatric Population								
CV-NCOV-009 (Planned) Phase 1	Healthy children and adolescents (5-17 years)	Europe and Latin America (5 countries) [10]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV	390	2 groups (3.3:1) • CVnCoV • Control vaccine	1Q21/ UNK*	• ELISA Spike IgG (all, 4 TP) • ELISA N-antigen IgG (all, 2 TP)	controlled, dose confirmation, age de-

Study ID (Status) Phase	Study Population	Region/ country [number of sites]	Primary Objective(s)	Sample size	Groups (ratio)	Study Start/ Duration	Laboratory Read-outs (Number of subjects, TimePoints)	Design (number of visits)
			• humoral immune response after 1 and 2 dose administrations of CVnCoV				• Virus neutralisation (all, 4 TP) • PCR	escalation (6)
CV-NCOV-010 (Planned Phase 2	Healthy children (6 months to 4 years)	Europe and Latin America (5 countries) [10]	• safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV • humoral immune response after 1 and 2 dose administrations of CVnCoV	540	2 groups (8:1) • CVnCoV • Control vaccine	2Q21/ UNK*	• ELISA Spike IgG (all, 4 TP) • ELISA N-antigen IgG (all, 2 TP) • Virus neutralisation (all, 4 TP) • PCR	controlled, dose finding, age de-escalation (6)
Concomitant Vaccination								
CV-NCOV-011 (Planned) Phase 3	Older adults (≥60 YOA)	Europe or Latin America& (2-3 countries) [3]	• safety and reactogenicity profile of 2 dose administrations of CVnCoV when co-administered with quadrivalent seasonal influenza vaccine • humoral immune response of 2 dose administrations of CVnCoV when co-administered with quadrivalent seasonal influenza vaccine • humoral immune response of the quadrivalent seasonal influenza vaccine when co-administered with CVnCoV	600	3 groups (1:1:1) • CVnCoV+ QIIV • CVnCoV • QIIV	4Q20 or 1Q21/ UNK*	• ELISA Spike IgG (all, 4 TP) • ELISA N-antigen IgG (all, 2 TP) • Haemagglutination inhibition antibodies (all, 2 TP) • PCR	controlled, non-inferiority (6)

AESI: adverse event of special interest; CMI: cell-mediated immunity; FIH: first-in-human; HCW: healthcare worker; IC: immunocompromised; N: nucleocapsid; n/a: not applicable; SAE: serious adverse event; PCR: polymerase chain reaction; pIMD: potential immune-mediated disease; TBC: to be confirmed; TP: timepoint; QIIV: quadrivalent inactivated influenza vaccine; UNK: unknown; YOA: years of age.

* Blinded safety follow-up for all SAEs, AESIs including pIMDs and pregnancies will be until end of the study at 12 months after the last dose, or until demonstration of efficacy leading to conditional marketing authorisation in any of the countries where the study is performed, whatever occurs first.

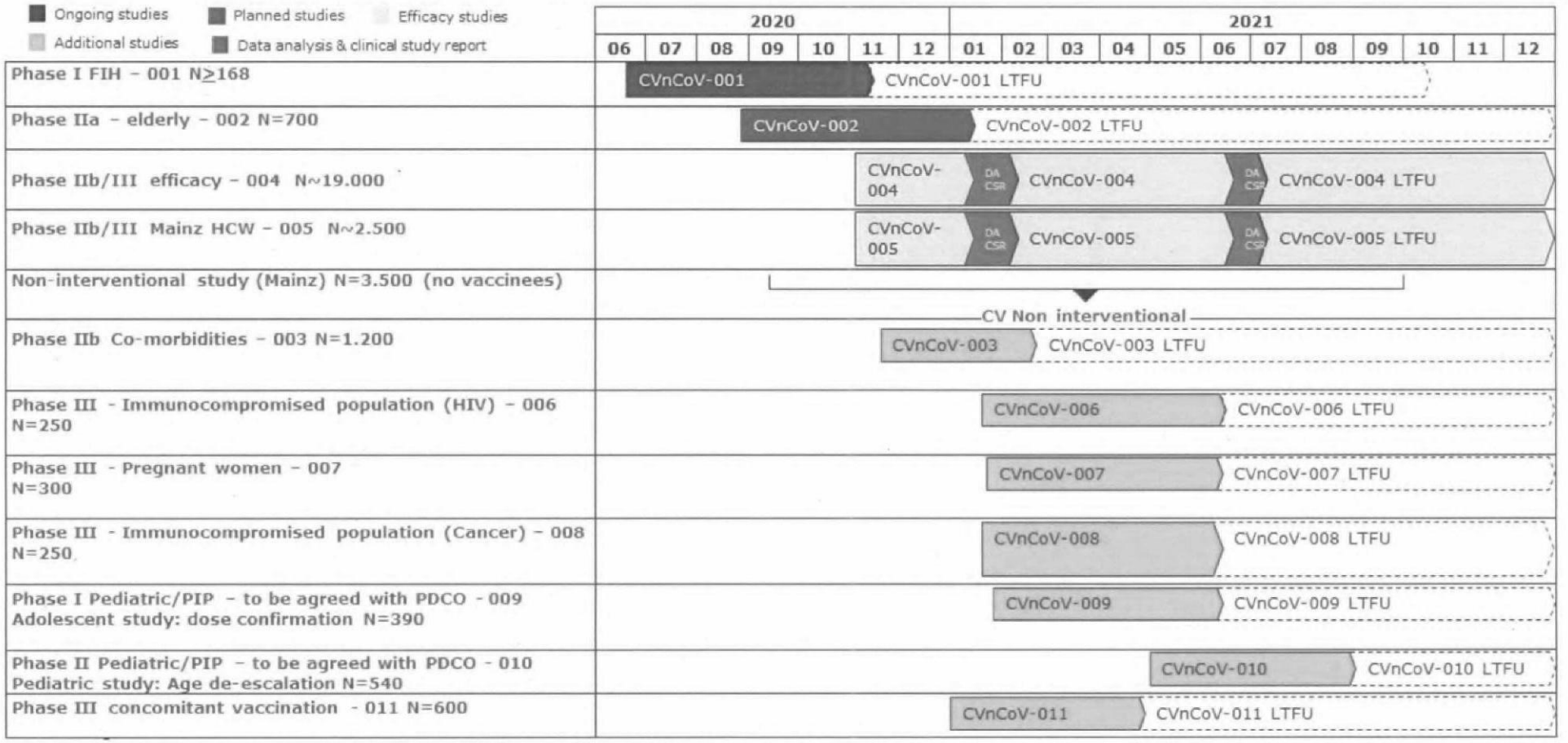
** Sponsor is P95 Epidemiology and Pharmacovigilance, for CureVac.

\# Based on current incidence in different countries: Europe (Belgium, Netherlands TBC), Latin America (Colombia, Dominican Republic, Mexico, Panama, Peru) and Asia (Bangladesh TBC). Further regions/countries might be added based on further evolvement of the pandemic.

& Europe (Belgium, the Netherlands, Finland) or Latin America (Brazil, Panama): depending on final start date: Northern or Southern Hemisphere

Figure 5: Draft Clinical Development Plan Diagram

This figure is for illustrative purposes, for example, for studies in special populations the timing is flexible based on data from CVnCoV-004, thus these studies may start in early 2021. The study in pregnant women will not start before DART study is completed.



CSR: Clinical study report; DA: Data analysis; FIH: First in human; FU: Follow-up; HCW: Healthcare Worker; HIV: Human Immunodeficiency Virus; LTFU: Long-term follow-up; PIP: paediatric investigation plan; PDCO: Paediatric Committee

D. Questions on Risk Management Strategy

Introduction

The Applicant wishes to obtain the EMA opinion on the planned Risk Management Strategy: namely, on whether the Summary of Safety Concerns is complete and correct, and on whether the planned PVP and the planned RMMs are suitable. Below is a general background, followed by specific questions and applicant's position.

Safety concerns

The list of safety concerns is based on the Safety Platform for Emergency vACcines (SPEAC) Priority List of Adverse Events of Special Interest for COVID-19 (CEPI 2020). The SPEAC list was followed with regard to the stated `Adverse Events of Special Interest (AESIs) relevant to vaccination in general` and as related to an insufficient immune response in vaccinees (Antibody-dependent enhancement (ADE) of CoV infection following immunisation).

Table 10 is identical to the one planned to constitute Table SVIII.1 (Summary of Safety Concerns) in the RMP.

Table 10: Summary of Safety Concerns

	Safety concern
Important identified risks	Reactogenicity following immunisation
Important potential risks	Antibody-dependent enhancement (ADE) of CoV infection following immunisation Anaphylaxis Thrombocytopenia Generalised convulsions Guillain Barré syndrome (GBS)
Missing information	Acute disseminated encephalomyelitis (ADEM) Vasculitides Safety in pregnant/ lactating women Safety in paediatric populations Safety in immunocompromised

CoV: coronavirus

Pharmacovigilance Plan (PVP)

In the following, the PVP (Part III of the RMP) for meeting the safety concerns through actions is briefly described. The current PVP is based on the current state of knowledge during the course of clinical development of CVnCoV. The list of adverse events of special interest (AESIs) identified (important identified risks, important potential risks and missing information) may change and the studies may also need to be adapted accordingly. For example, if reactogenicity is found not to be of concern after the clinical studies are finished, pharmacovigilance (PV) studies addressing reactogenicity may not be needed.

The following *routine PV activities* are planned (Table 11):

- **Enhanced passive surveillance**

  Enhanced passive surveillance to evaluate the reactogenicity within 7 days following immunisation as well as AESIs in the general population of 18-64 years old (adults), > 65 years old (elderly), pregnant/lactating women and the immunocompromised. Observed-to-Expected analysis will be conducted for AESIs with information on background rates obtained from the literature or appropriate external sources. Targeted follow-up questionnaires will be developed for all important identified risks, potential risks and missing information.

The following *additional PV activities* are planned (Table 11):

- **Post-authorisation Safety Study**

A post-authorisation safety study (PASS) to evaluate the safety profile of CVnCoV in the general population of 18-64 years old (adults) and > 65 years old (elderly). At present, it is unknown which countries will use CVnCoV in their mass vaccination programme. When/If the vaccine will be used in a country for which a research-ready database is available, an observational retrospective database study will be conducted. A database is considered research-ready when it has been successfully used for research before, when it is suited for near-real time monitoring (i.e. events must be available for analysis within 3 months after onset) and when, in case multiple COVID-19 vaccines are used within the country, it captures vaccination information at brand level. Otherwise, a cohort event monitoring (CEM) study will be performed. In the CEM study, vaccinated subjects will be followed prospectively and a self-controlled case-series (SCCS) design will be used to evaluate increases in risk. The aim of this study is to monitor pre-defined adverse events associated with the routine use of the vaccine under real life conditions. The sample size of such a study is evaluated to be approximately 3000 subjects.

- **Pregnancy Registry**

Although a clinical study is foreseen to be performed likely starting 1Q2021 (CV-NCOV-007), the follow-up will likely be ongoing and safety in off-spring therefore not fully assessed at the moment of conditional marketing authorisation. Since it is expected that, in case of conditional marketing authorisation, the vaccine might be primarily used in Health Care Workers, this will comprise women of childbearing potential. Therefore, this observational study to evaluate the safety profile of CVnCoV in pregnant women and their offspring will likely need to be set up. Even in the case of a contra-indication, first trimester CVnCoV exposure might occur as many pregnancies occur in women not seeking to become pregnant. Enrolment into the registry will be voluntary. Pregnancies will be monitored and outcomes ascertained through questionnaires. The aim of this study is to evaluate pregnancy outcomes of miscarriage, stillbirth, prematurity, congenital malformations and low birth weights among infants of women who received at least one dose of CVnCoV within one month prior to conception or at any time during pregnancy.

Clinical trial among immunocompromised (IC) people that are IC due to primary IC conditions, or secondary due to certain diseases (e.g. haematological malignancies, HIV) or treatments for underlying diseases (e.g. transplant, chemotherapy, certain biologicals to treat auto-immune diseases, and others), are at increased risk of COVID-19 disease and should therefore be able to benefit from vaccination, even if it is known that people with such conditions or treatments do not always mount sufficient immune response or protection after vaccination However, during the initial clinical development, IC subjects will be excluded from the clinical trials, in order to assess safety, immunogenicity and efficacy in a general population not confounded by a population that potentially will not be protected to the same level by the vaccine and/or might need a higher dose or additional vaccinations. Nevertheless, as part of the clinical development plan, two specific IC populations are planned to be studied, i.e. HIV-infected individuals (CV-NCOV-006) and cancer patients (CV-NCOV-008). The applicant believes that providing acceptable safety data in these two distinct IC populations, combined with demonstration of a robust immune response, comparable to what is observed in non-IC subjects, should prevent a contra-indication or warning in the label for use in overall IC populations.

The following *post-authorisation efficacy study* is planned (Part IV of the RMP; Table 11):

- **Test-Negative case-control study for vaccine effectiveness (VE) and studying ADE**

A multi-centre, post-licensure, prospective test-negative case-control study by health care setting (primary care and hospital setting). In this design, the history of CVnCoV vaccination among individuals who present to a health facility with suspected COVID-19 and whose diagnosis is virologically confirmed to be COVID-19 (i.e. test positive in RT-PCR analysis of nasopharyngeal swab material; cases) is compared to the history of CVnCoV vaccination among suspected cases who are diagnosed not to have COVID-19 (i.e. test negative; controls). The aim of this study is to investigate, in subjects eligible for vaccination, the effectiveness of vaccination with CVnCoV in preventing virologically-confirmed COVID-19, by healthcare setting and by severity.
This design will also be used to study antibody-dependent disease enhancement (ADE) by monitoring risk of progression to severe disease, in vaccinated and unvaccinated COVID-19 cases, and by increasing time since vaccination.

Table 11: Planned studies and the safety concerns addressed

Study	Summary of objectives	Safety concerns/missing information addressed
Enhanced passive surveillance	To monitor vaccine safety in the general and elderly population, pregnant/lactating women and in the immunocompromised	Reactogenicity Anaphylaxis Thrombocytopenia Generalised convulsions Guillain Barré syndrome (GBS) Acute disseminated encephalomyelitis (ADEM) Vasculitides
Post-authorisation safety study	To monitor vaccine safety in the general and elderly population	Anaphylaxis Thrombocytopenia Generalised convulsions Guillain Barré syndrome (GBS) Acute disseminated encephalomyelitis (ADEM) Vasculitides
Pregnancy registry	Study the effect of vaccination during pregnancy and lactation. Outcomes are maternal morbidity/mortality, miscarriage/stillbirth, prematurity and congenital anomalies	Safety in pregnant/ lactating women
Clinical trials among immune-compromised	Study vaccine safety in a subpopulation of immunocompromised subjects, including HIV-positives and cancer patients	Safety in immunocompromised
Test-negative case-control study for vaccine effectiveness (VE)	Study vaccine effectiveness and ADE by monitoring the risk of progression to severe disease in vaccinated and unvaccinated COVID-19 cases, and by increasing time since vaccination	Vaccine effectiveness Antibody-dependent enhancement (ADE) of SARS-CoV-2 infection following immunisation

The planned routine risk minimisation measures (RMMs) are:

- SmPC: the list of safety concerns will be included and described in the SmPC (with adapted language in Section 4.8). After end of the clinical trials, this list may be reduced.
- Package leaflet
- Labelling
- Pack size and design
- Legal (prescription) status

No additional RMMs are planned.

Question 17

Does EMA agree with the Applicant´s Summary of Safety Concerns?

Applicant's Position

The Summary of Safety Concerns for the CVnCoV RMP is aligned with the SPEAC Priority list of Adverse Events of Special Interest: COVID-19 (CEPI 2020). During the course of the clinical development programme, the Applicant did not yet detect any signals for events that justify addition to the predefined SPEAC list. The SPEAC list was followed with regard to the stated `Adverse Events of Special Interest (AESIs) following vaccination in general` and as related to an insufficient immune response in vaccinees (Antibody-dependent enhancement (ADE) of CoV infection following immunisation). As previously mentioned, this list is subject to changes following the monitoring of safety in the ongoing clinical development programme.

Question 18

Does EMA agree with the Applicant´s Pharmacovigilance Plan (PVP)?

Applicant's Position

As first additional PV activity, a PASS will be conducted to evaluate the safety profile of CVnCoV in the general population of 18-64 years old (adults) and > 65 years old (elderly). However, at present, it is unknown which countries will use CVnCoV in its mass vaccination programme. When/if the vaccine will be used in a country for which a research-ready electronic health record (EHR) database is available, an observational retrospective database study will be conducted. An EHR database is considered research-ready when it has been successfully used for research before, when it is suited for near-real time monitoring (i.e. events must be available for analysis within 3 months after onset) and when, in case multiple COVID-19 vaccines are used within the country, it captures vaccination information at brand-level. Large EHR databases are used more and more to study outcomes of vaccination. The large population size covered by EHR databases allows for the study of rare events and, as they are embedded within clinical practice, EHR databases offer the potential to study real-world vaccine effects relatively efficiently from both resource and time perspectives (Schneeweiss and Avorn, 2005). Depending on the CVnCoV uptake, an appropriate study design will be chosen. It is anticipated that the SCCS method will be used. This is a study design for which individuals act as their own controls; it has the advantages that no separate controls are required and any fixed confounder is automatically controlled for (Farrington et al, 2018). Calendar time (as the SARS-CoV-2 infections strongly fluctuate over time) is a relevant time varying factor and will be accounted for in the analysis. The major drawback of this approach is that it requires a research-ready database. Not all countries have such databases available, and especially the requirements for near-real time monitoring are stringent (Bollaerts et al, 2019).

If EHR databases suited for near-real time monitoring are unavailable for the countries where CVnCoV will be used, a cohort event monitoring (CEM) study will be performed instead. CEM is an intensive method for post-marketing safety surveillance that uses an observational prospective cohort design, capturing all adverse events that occur in a defined group of individuals (the cohort) who are exposed to the newly marketed product during the course of routine clinical practice (Suku et al, 2015). CEM has been used for the monitoring of vaccines, including the influenza H1N1 pandemic vaccine (Torre et al, 2019). For the safety monitoring of CVnCoV, subjects will be enrolled in the cohort at the time of their first vaccination. Depending on where CVnCoV will be administered, vaccinees will be enrolled by general practitioners (GPs), vaccination clinics or occupational medicine clinics. At the initial encounter, demographic information, past medical history, medication use and presenting symptoms will be captured. Patients will then be followed-up to record any new adverse event that began after CVnCoV vaccination. Depending on the country where the study will be implemented, the mode of follow-up might be different (e.g. web-based surveys, mobile phone applications, household visits, follow-up calls). The information collected during follow-up will be complemented with medical information obtained from primary care or hospital records. An SCCS analysis will be used to evaluate increases in risk. The sample size of such a study is evaluated to be approximately 3000 subjects. The major advantages of CEM is that it can be implemented everywhere (including in resource-low settings), that information can be collected in real-time and that the primary data collection allows close monitoring of any adverse event of interest. The major disadvantage, compared to EHR databases, is its smaller sample size.

In addition, a pregnancy registry will be set up to evaluate the safety profile of CVnCoV in pregnant women and their offspring. Even in the case of a contra-indication, first trimester CVnCoV exposure might occur as many pregnancies occur in women not seeking to become pregnant. This is particularly relevant for COVID-19 vaccines as healthcare workers, including women of childbearing age, are likely to be prioritised for vaccination. EHR databases are generally not suited for studying vaccine safety in pregnant women as they do not routinely record evidence on pregnancy or provide child-mother linkages. Also, important pregnancy outcomes such as gestational age at birth and birth weight are rarely available. Therefore, a pregnancy registry (that is, observational exposure-registration and follow-up programme of pregnancy outcomes) will be conducted. Women who received at least one dose of CVnCoV within one month prior to conception or at any time during pregnancy will be enrolled into the registry on a voluntary basis. Pregnancies will be monitored and pregnancy outcomes of major congenital malformations, pre-term delivery, or low birth weight will be ascertained through dedicated questionnaires. A comparison group external to the study will be used to assess potential increases in risk. Ideally, this external comparison group will be from a population-based surveillance system, from published background rates of individual outcomes, or from other pregnancy exposure registries. Pregnancies in women enrolled retrospectively (after the outcome of the pregnancy is known) will be analysed separately from pregnancies in women followed-up prospectively to distinguish the potential bias of (retrospective) reporting adverse pregnancy outcomes.

In order to assess CVnCoV in specific additional populations at risk for COVID-19, namely IC populations, clinical studies are planned in two different populations i.e. HIV-infected individuals and cancer patients. While HIV-infected individuals are IC due to the underlying disease, most cancer patients are IC mainly due to their treatment such as chemotherapy.

Sub-Saharan Africa has not been spared from the COVID-19 pandemic. As this region of the world is hit hardest by HIV/AIDS (eastern and southern Africa represent >50% of the world's people living with HIV), a global SARS-CoV-2 vaccine will also need to be effective in people living with HIV/AIDS. A study in HIV-positive adults will therefore assess safety, reactogenicity, and immunogenicity in these populations.

The additional selected IC population, i.e. patients with cancer, is considered to be another important target population for COVID-19 vaccination.

These studies will allow safety assessment of CVnCoV in more fragile populations. It will also learn if CVnCoV is able to overcome the IC condition, or if either an additional vaccination, or a higher dose administered as per the classical two-dose schedule should be implemented in IC people. The applicant considers it is important to provide Health Care Practitioners with data in these populations at risk early, and expects that information on the needed dose level or schedule to ensure a robust immune response while providing an acceptable safety profile will allow extrapolation to other IC populations, and lead to early implementation of vaccination and thus protecting this important overall population at risk. Nevertheless, the proposed enhanced passive surveillance will include IC patients so as to complement data in these populations.

The post-authorisation efficacy study (PAES) will consist of a test-negative case-control study, taking advantage of the existing sentinel surveillance systems for influenza-like illness (ILI, in primary care settings) and severe acute respiratory illness (SARI, in hospital settings). These health facility-based surveillance systems have been mainly used for influenza to monitor its virus activity, burden of disease and vaccine effectiveness. Test-negative case-control designs have often been used in conjunction with ILI/SARI surveillance to obtain vaccine effectiveness estimates. The test-negative case control design is a particular case-control design in which controls are selected from individuals who share similar clinical symptoms with the case, but who are not infected with the organism targeted by vaccination. This method was proposed in order to provide an efficient method for evaluating influenza vaccine effectiveness within a sentinel surveillance system (Skowronski et al, 2007). Case-control studies in general have the advantage over cohort studies of requiring less samples, which is particularly advantageous when the infection is less common and when there is interest to obtain evidence quicker. By additionally selecting controls among those seeking healthcare, healthcare seeking bias is minimised. Given the similarities between influenza and COVID-19 in clinical presentation, specimen types and laboratory testing platforms, the ILI/SARI sentinel surveillance systems are currently being used to monitor COVID-19 across the world. These systems are also well suited to monitor the real-world vaccine effectiveness of the future COVID-19 vaccines and several initiatives have been taken to prepare for this (ACCESS (EMA 2020), I-MOVE (I-MOVE 2020), CDC). To evaluate the effectiveness of COVID-19 vaccines, patients presenting with ILI/SARI will be categorised as cases if they test positive for SARS-CoV-2, and as controls if they test negative for SARS-CoV-2. To evaluate the effectiveness of CVnCoV, CureVac will collaborate with public health authorities, reference laboratories and clinical investigators or study networks for the implementation of test-negative case-control studies. RT-PCR tests with high sensitivity and specificity will be used to minimise disease misclassification bias. In addition, subjects with other vaccine preventable diseases (e.g. influenza or pneumococcal disease) will be excluded from the control group to minimise bias resulting from differences in the propensity to get vaccinated (e.g. if those vaccinated with a COVID-19 vaccine are more likely to have received influenza or pneumococcal vaccination, the CVnCoV vaccine effectiveness will be underestimated).

The test-negative case-control study evaluating the CVnCoV effectiveness will also be used to study antibody-dependent disease enhancement (ADE) of SARS-CoV-2 following immunisation. The hypothesis, that prior exposure to non-neutralising virus-specific antibodies (either through natural infection or vaccine-induced) might enhance disease severity upon re-infection, has emerged as a hypothesis to explain the severe clinical manifestations associated with COVID-19. The hypothesis of enhanced disease following CVnCoV immunisation will be investigated by studying the effect of CVnCoV in preventing progression to severe disease (vaccine effectiveness for progression, VEP) (Halloran et al, 2010). The COVID-19 cases identified within the test-negative case-control study will be utilised to estimate progression to severe disease by comparing the clinical profiles and the risks of a case being severe (according to pre-defined case definitions) in vaccinated and unvaccinated cases. Additionally, the progression risks to severe disease will be investigated by time since vaccination. With increasing time since vaccination, it is anticipated that the vaccine-induced neutralising antibodies decay, and consequently, the risk of progression to severe disease increases.

Question 19

Does the EMA agree on the Applicant´s risk minimisation measures (RMMs)?

Applicant's Position

Routine RMMs are planned, but *no additional* RMMs are planned.

In the absence of signals from the clinical development programme to date, all risks or missing information are based on theoretical concerns. Hence it is envisioned that no additional risk minimisation measures are needed. This position may change in the course of the monitoring of safety in the ongoing clinical development programme.

E. Regulatory Questions

Question 20

In the context of the COVID-19 Pandemic, would the EMA agree that a Conditional Marketing Application/Conditional Marketing Authorisation would be appropriate based our current development plan?

Applicant's Position

This request is based on precedent for conditional marketing authorisation for Remdesivir on 3 July 2020. Like Remdesivir, a proposed marketing authorisation of CVnCoV is in the interest of public health because this vaccine addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required for a prophylactic vaccine.

Question 21

Would a rolling submission process, pre-defined (per applicant's position) with access to consultation throughout the procedure be acceptable to the EMA to expediently bring CV07050101 to market?

Applicant's Position

Would the EMA agree with the proposed rolling clinical submission plan for proposed Conditional Marketing Application and Standard Marketing Authorisation Application as follows?

Proposed Conditional Marketing Application	**Standard Marketing Authorisation Application**
-001 interim abbreviated CSR	-001 CSR (with 10 months safety follow-up)
-002 interim abbreviated CSR	-002 CSR (with 8 months safety follow-up)
-004 (interim analysis) abbreviated CSR	-004 CSR (with 6 months safety follow-up)
-003 interim abbreviated CSR	-003 CSR (with 6 months safety follow-up)
-005 interim abbreviated CSR	-005 CSR (with 6 months safety follow-up)
	-006 interim abbreviated CSR
	-007 interim abbreviated CSR
	-008 interim abbreviated CSR
	-009 interim abbreviated CSR
	-011 interim abbreviated CSR
Interim 2.5 and 2.7	2.5 and 2.7 (with 6 months safety follow-up from -001, -002, -003, -004 and -005)
Safety (including VDE) as well as efficacy will be pooled over different studies as per a predefined pooling strategy. This will include (for efficacy) all studies from -001 to -005; safety pooling will be done as per the population under study (age, underlying conditions)	Safety (including VDE) as well as efficacy will be pooled over different studies as per a predefined pooling strategy. This will include (for efficacy) all studies from -001 to -011; safety pooling will be done as per the population under study (age, underlying conditions)

CSR: Clinical study report; VDE: vaccine-dependent disease enhancement

Question 22

Based on the proposed clinical development plan, should the data support it, would the EMA agree with the proposed indication for the prevention of virologically confirmed COVID-19 disease in individuals 18 years of age and above?

Question 23

Would the EMA comment on recommended endpoints for prevention of COVID-19 infection, for an indication of prevention of virologically confirmed COVID-19 disease and infection in individuals 18 years of age and above?

Applicant's Position Questions 22 and 23

Please refer to applicant's position for Questions 12 and 13.