10. Technical offer

CUREVAC
the RNA people®

10.1.

2. QUALITY

2/1.1 Roadmap towards starting clinical trials in 2020

The first in human Phase 1 study was initiated in June 2020 after approval by the relevant competent authorities in Germany and Belgium. The study (CV-NCOV-001) is ongoing and definition of the selected dose for the pivotal Phase 2b/3 trial (CV-NCOV-004) is scheduled for September 2020 based on safety and immunogenicity data of tested doses.

Based on the above CureVac confirms that it has already entered into clinical trials as required by this tender since June 2020.

Evidence:

- Clinical Trial Approval for Belgium and Germany (see attached)
- Interim results shared in Scientific and technical presentation (see attached)

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Paul-Ehrlich-Institut Postfach 63207 Langen

CureVac AG

5.1.2e

Schumannstr. 27
Frankfurt 60325

EudraCT-Nr. 2020-001286-36
Vorlage-Nr.: 4121/01
Bearbeiter/in: 5.1.2e
Referatsleiter klin. Prüfungen/Ref. S5
Abtlg. Arzneimittelsicherheit
Telefon / Phone 5.1.2e
Fax
E-Mail 1.2@pei.de

16.06.2020

Genehmigung der klinischen Prüfung gem. § 42 Abs. 2 AMG
Kurz-Titel: CV-NCOV-001
Ihr Antrag vom 29.05.2020

Bescheid

Die klinische Prüfung mit dem Studientitel:

COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-inhuman, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

zur Prüfung der Prüfsubstanz CVnCoV wird unter dem Hinweis in der Anlage genehmigt.

Die Entscheidung über die Gebühren ergeht gesondert.

Rechtsbehelfsbelehrung:

Gegen diesen Bescheid kann innerhalb eines Monats nach Bekanntgabe Widerspruch erhoben werden. Der Widerspruch ist beim Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Str. 51-59, 63325 Langen, schriftlich oder zur Niederschrift einzulegen.

Mit freundlichen Grüßen
Im Auftrag

Dieser Bescheid wurde maschinell erstellt und ist ohne Unterschrift gültig

5.1.2e

Anlage zum Bescheid zur Genehmigung der klinischen Prüfung vom 16.06.2020

Prüfsubstanz: CVnCoV

EudraCT-Nr.: 2020-001286-36 **Vorlage-Nr.:4121/01**

Studientitel: COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-inhuman, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

Hinweis:

Charta des DSMB:

Es wird eingeräumt, dass der Sponsor die Verantwortung für seine Prüfsubstanz und die klinische Prüfung trägt. Der Antragsteller sollte jedoch bei abweichenden Positionen zwischen Sponsor und DSMB die Empfehlungen des DSMB beim Paul-Ehrlich-Institut einreichen.

famhp
federal agency for medicines and health products

Federal Agency for Medicines and Health Products
Eurostation II - Place Victor Horta 40/40
1060 BRUSSELS
www.fagg.be - www.afmps.be

DG PRE / R&D Division

5.1.2e
Tel. : +32 (0)2 5.1.2e
Fax : +32 (0)2
e-mail : 5.1.2e @fagg.be

CureVac AG
5.1.2e
Schumannstr. 27
60325 Frankfurt
Germany

Your letter from	Your reference	Our reference	Annex	Date
		FAGG/R&D/VDC		

Onderwerp
Titre de l'objet
Subject

Goedkeuring van een klinische proef op 17/06/2020
Approbation d'un essai clinique le 17/06/2020
Authorisation of a clinical trial dated 17/06/2020

COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

EudraCT: 2020-001286-36

Chère Madame,

Conformément à l'article 12 de la Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine, j'ai décidé d'autoriser l'essai clinique ci-dessus mentionné.

Cependant, un suivi doit être apporté aux points mentionnés en annexe.

Salutations sincères,

Pour la Ministre des Affaires Sociales, de la Santé publique, de l'Asile et de la Migration

Geachte Mevrouw,

In overeenstemming met artikel 12 van de wet van 7 mei 2004 inzake experimenten op de menselijke persoon, heb ik besloten de hierboven vermelde proef goed te keuren.

Niettemin moet er gevolg gegeven worden aan de opmerkingen vermeld in bijlage.

Met de meeste hoogachting,

Voor de Minister van Sociale Zaken, Volksgezondheid, Asiel en Migratie

5.1.2e 5.1.2e

Unofficial translation

In accordance with article 12 of the Law of 7 May 2004 concerning experiments on the human person, I have decided to authorise the above mentioned clinical trial. However, the points as mentioned in annex are to be followed up.

Annex

Quality

Commitment

CTA 2020-001286-36 is approved with the following commitment:

In view of the updated quality data with respect to the clinical batch CCV0520-A, the trial is accepted. No notification or further substantial amendment should be submitted when updating the stability or expiration data in the IMPD if there is no quality concern. The adjustment of the shelf life must be done according to the stability plan which is described in the IMPD. The product can be administered to humans, but if quality concerns arise, they need to be notified immediately and the treatment should be stopped, if necessary.

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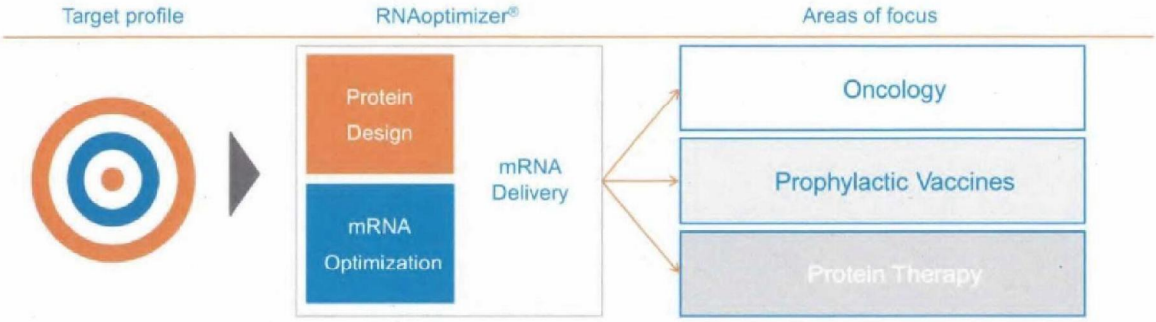
RNAoptimizer® Creates Unique, IP-protected Product Candidates

1 Identification of a target expression profile for each mRNA product candidate

2 RNAoptimizer® provides optimal mRNA solutions for each target indication

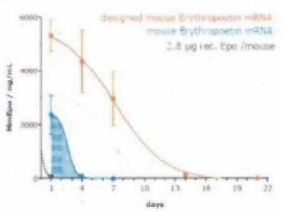
3 The optimization process allows us to pursue new and exclusive IP protection for each product candidate across our focus areas and proprietary technologies



Protein Design: Enables the Optimization of Specific Properties of the Encoded Protein

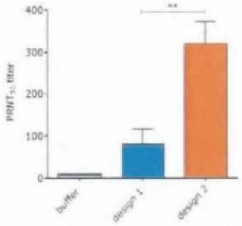
- Ability to modify amino acid sequence to optimize protein properties including half-life, stabilization of tertiary structure, oligomerization, secretion and immunogenicity
- Bespoke and multi-factorial to support distinct functions and requirements of the specific target protein

Extended half-life of secreted protein



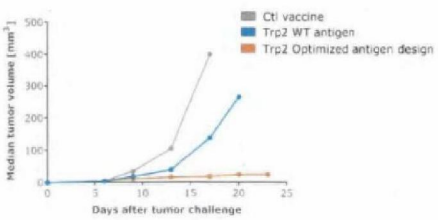
Relevant serum titers of functional Epo and different pharmacokinetic profiles

Oligomerization



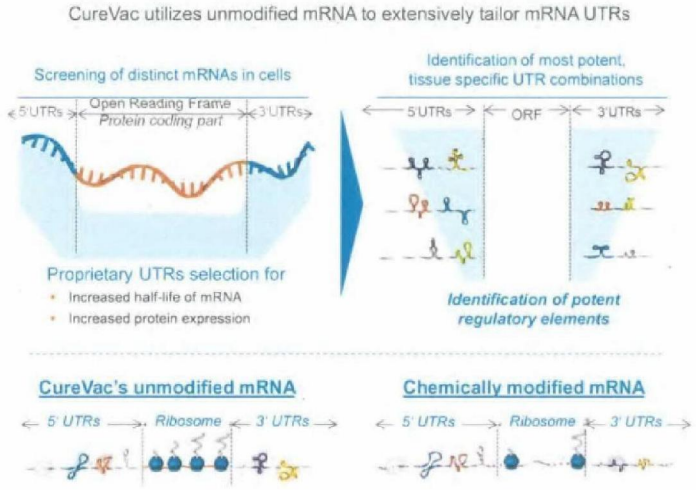
Higher induction of neutralizing antibodies demonstrated via optimized mRNA

Modified immunogenicity

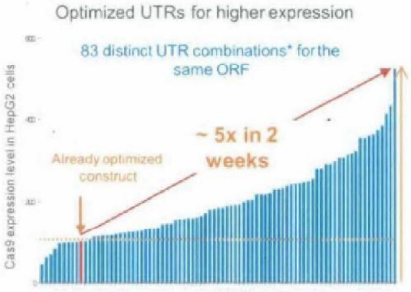


Tumor growth inhibited in murine melanoma model

mRNA Optimization: Optimizes *Unmodified* mRNA to Enhance Protein Expression and Stability

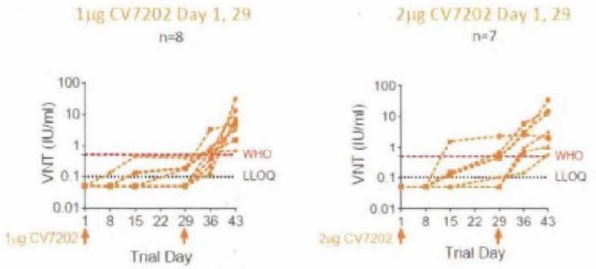


- mRNA optimization process designed to generate the most efficacious mRNA by optimizing translation, stability and immunogenicity
- Ability to optimize six elements of mRNA including 5' cap, 5' UTR, ORF, 3' UTR, and 3' poly-A tail and 3' end



CureVac's Rabies Vaccine CV7202 Induces Protective Antibody Titers at Dose Levels of 1µg and 2µg

CV7202 –Rabies Vaccine –1µg dose x 2 (n=8); 2µg dose x 2 (n=7)

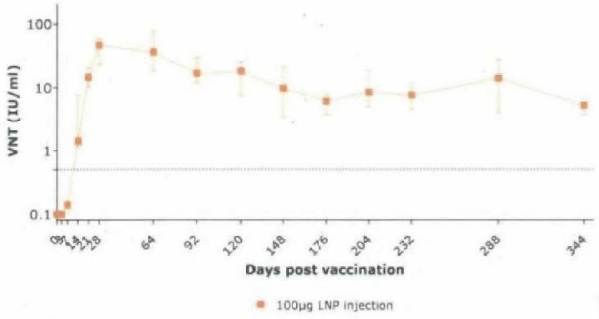


Preliminary data
Values <LLOQ are shown as half LLOQ

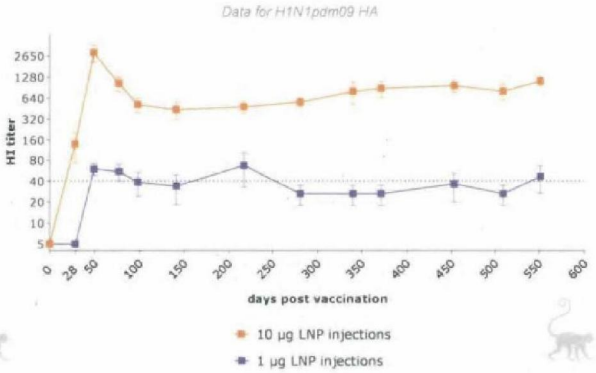
- All volunteers were protected after the 2nd administration of 1µg or 2µg rabies vaccine
- Detectable VNTs as early as 8 days after 1 administration in some subjects
- After two IM doses of 1µg or 2µg, 28 days apart, all subjects with available data had VNTs above the ≥0.5IU/mL WHO recommended antibody level, 14 days after Dose 2 (Day 43)
- Vaccinations were well tolerated
- No SAEs reported
- Durability of response: currently available follow-up at 6 month show stable antibody titers

Long Durability of Response Demonstrated at All Doses Across Different Vaccines

Rabies mRNA vaccine induced high titers of virus-neutralizing antibodies (VNT) after a single IM injection



mRNA flu vaccine demonstrated strong and durable immunogenicity in non-human primates (NHP)



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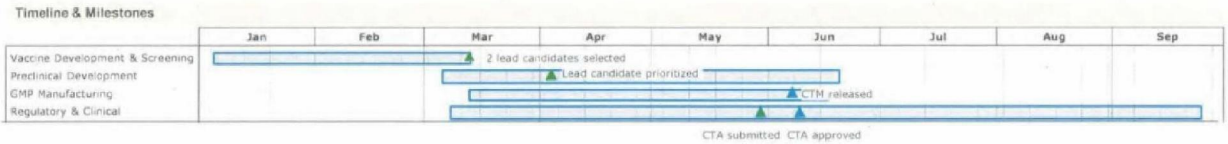
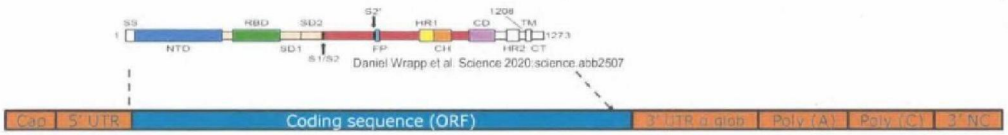
CureVac's SARS-CoV-2 Vaccine Program – CVnCoV Development Status

- Clinical candidate CVnCoV selected based on biological properties and manufacturability
- Characterization of immunogenicity and safety evaluated in vitro and in vivo (mice and rats)
- Manufacturing in new GMP III facility (Tuebingen, Germany) and new fill-and-finish at CMO (Polymun, Austria)
- Approval of First-in-Human trial (CV-NCOV-001) by German PEI and Belgian FAMHP – 1st subject vaccinated on June 19th
- Interaction with EMA task force (ETF) to define path to approval:
  - Briefing document submitted on 14-Aug – Response expected by 08-10 Sep by ETF



CVnCoV Encodes the Full-Length Spike (S) Protein as Antigen



	R number	ORF	Codon usage
CVnCoV Clinical Candidate	R9515	Full length stabilized S protein	CureVac proprietary algorithm

Characteristics of the Coronavirus S protein: Trimer forming glycoprotein on the viral surface
Parallel to previously developed antigens at CureVac (influenza HA, rabies G, RSV F, HIV-1 Env)

Employing S protein as an antigen: Only significant target for neutralizing antibodies for Coronaviruses
→ S protein has been widely used in the context of SARS and MERS vaccine candidates

Stabilized version published for MERS and SARS: designed to prevent the transition from the pre-fusion to post-fusion states → Candidate constructs were designed to increase the induction of VNT over binding antibodies

Characterization of mRNA-Induced Immune Responses

in vitro characterization of IFNα induction

- Tested doses: Mouse Serum: 4µg, 1µg, 0.25µg
  Human PBMCs: 5µg/1x10^6 cell

in vivo characterization of humoral and cellular responses

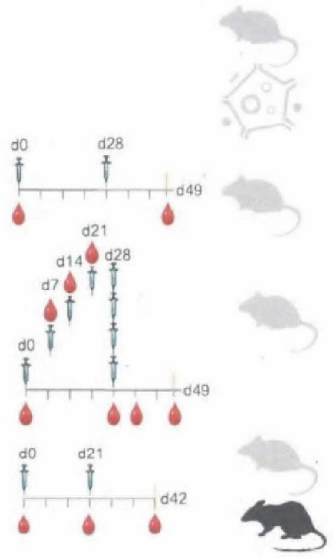
- Tested dose: **2 µg**

Impact of vaccination schedule

- Tested dose: **2 µg**
- Vaccination schedules: time interval between
  1st and 2nd vaccination: **4, 3, 2 or 1 week**

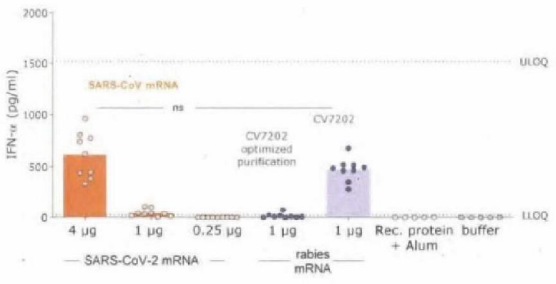
Assessment of dose range

- Mice - tested dose range: **0.25 µg, 1 µg, 4 µg**
- Rats - tested dose range: **0.5µg, 2µg, 10µg, 20µg, 80µg**

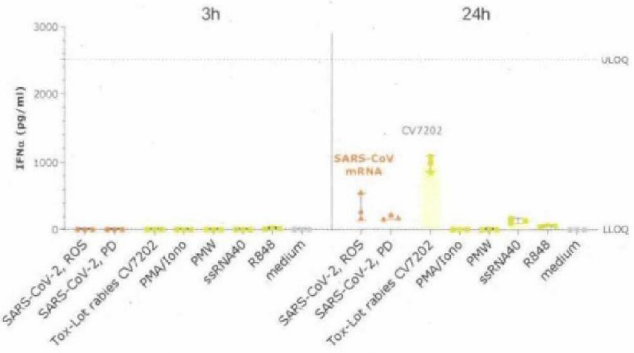


Characterization of IFNα induction: CVnCoV induces lower levels of IFNα compared to CV7202*

IFNα induction mouse serum 14h p.i.



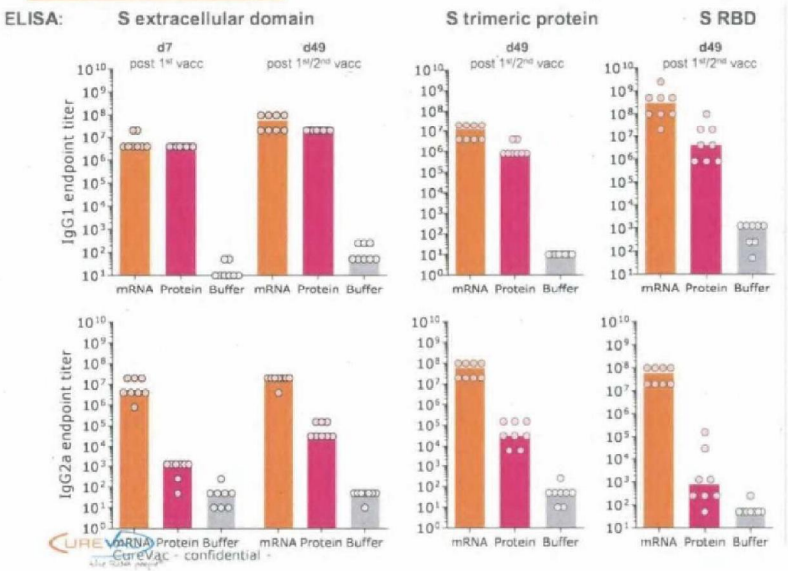
IFNα induction in hPBMCs

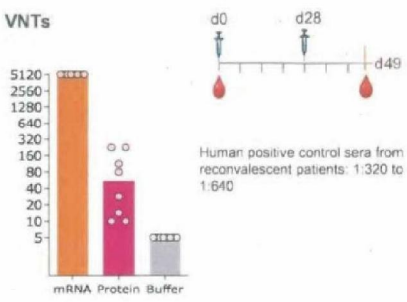


- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Evaluation: IFNα levels via ELISA

*CV7202 refers to the material used in the Rabies clinical trial 104

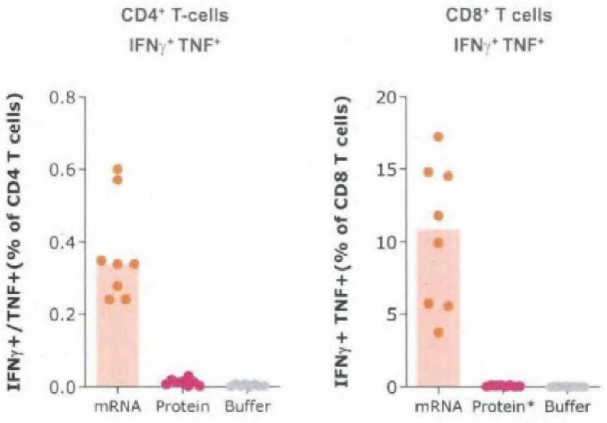
Characterization of humoral and cellular responses: CVnCoV induces antibody responses with strong binding to the RBD

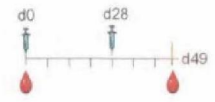




- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Evaluation:
  - ELISA: coating with SARS-CoV-2 S extracellular domain, trimeric protein or RBD (receptor binding domain)
  - VNTs: Cytopathic effect (CPE) based, microneutralization at VisMederi

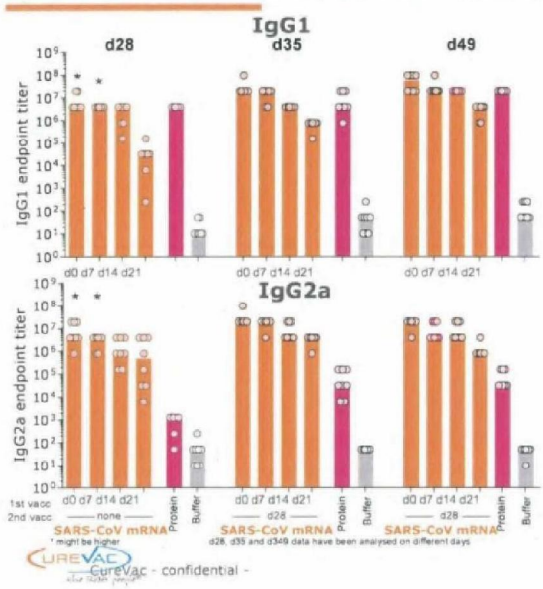
Characterization of humoral and cellular responses: CVnCoV induces high levels of double positive T-cell responses

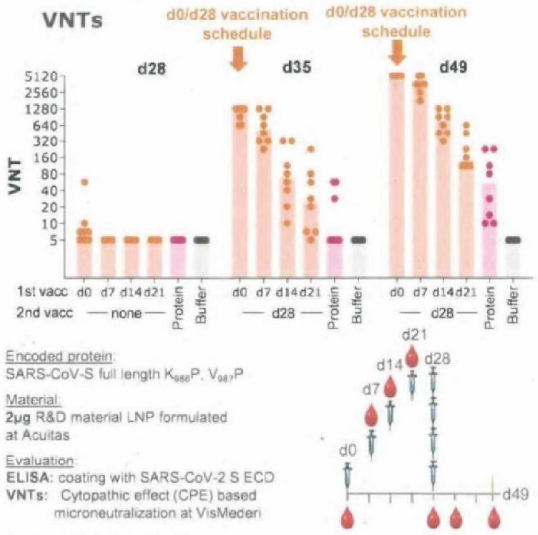




- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Evaluation: ICS stimulated with S full length library 11 mers 15 overlapping

Impact of vaccination schedule:
A 4-week vaccination schedule provides the best immune response

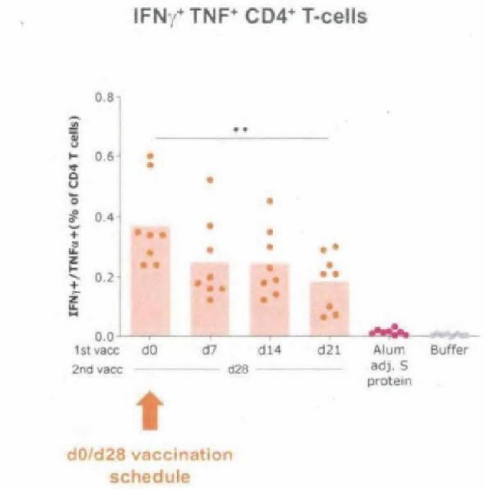


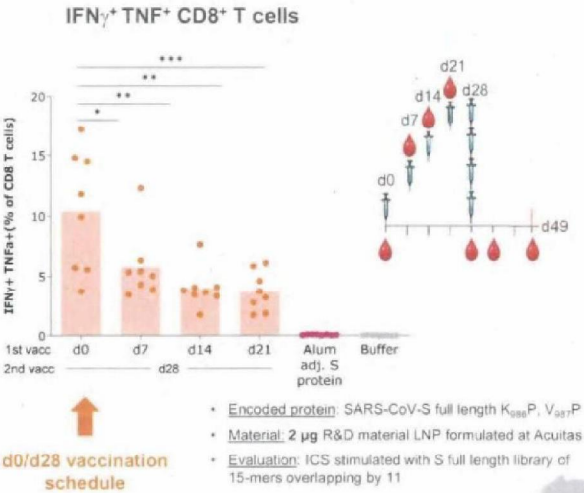


- Encoded protein:
  SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Material:
  2µg R&D material LNP formulated at Acuitas
- Evaluation:
  ELISA: coating with SARS-CoV-2 S ECD
  VNTs: Cytopathic effect (CPE) based microneutralization at VisMederi

Human positive control sera from reconvalescent patients: 1:320 to 1:640

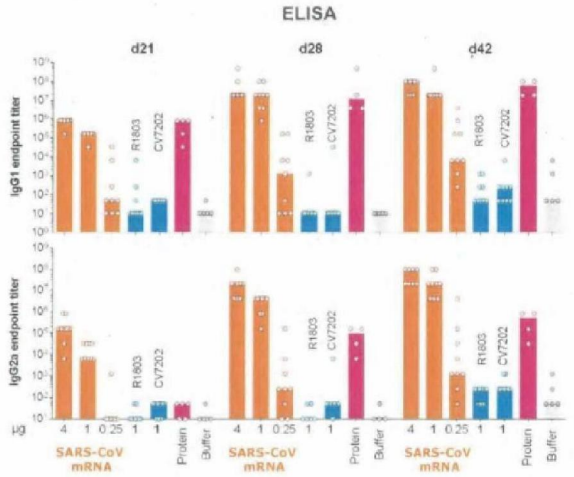
Impact of vaccination schedule:
T cell responses in mice increase with longer vaccination schedule

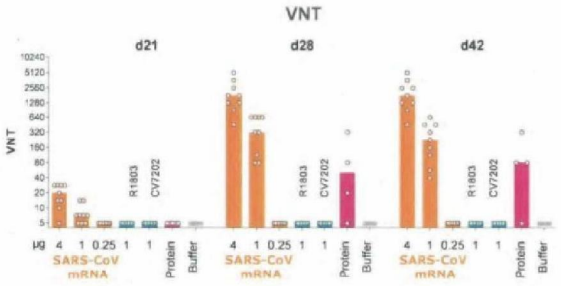




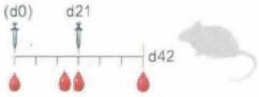
- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Material: **2 µg** R&D material LNP formulated at Acuitas
- Evaluation: ICS stimulated with S full length library of 15-mers overlapping by 11

Assessment of dose range – mice:
CVnCoV induces robust immune responses at 1 µg and above

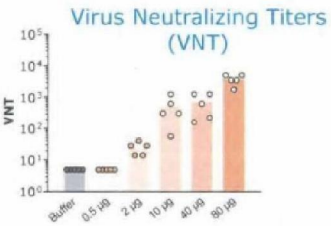


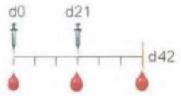


- Encoded protein: SARS-CoV-2 S full length $K_{986}P$, $V_{987}P$
- Material: PD material LNP formulated at Polymun
- Evaluation:
  ELISA: coating with SARS-CoV-2 S ECD
  VNTs: Cytopathic effect (CPE) based microneutralization at VisMederi
  Human positive control sera from reconvalescent patients: 1:320 to 1:640

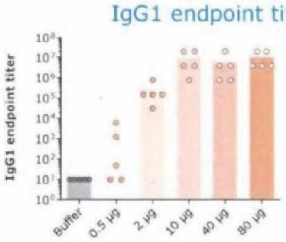


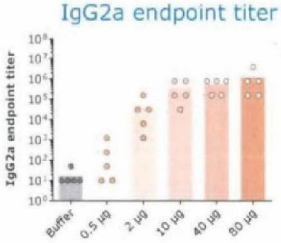
Assessment of dose range – rats:
CVnCoV induces dose-dependent immune responses





- Encoded protein: SARS-CoV-2 S full length $K_{986}P$, $V_{987}P$
- Evaluation:
  ELISA: coating with SARS-CoV-2 S ECD
  VNTs: Cytopathic effect (CPE) based micro-neutralization at VisMederi, Italy





Human positive control sera from reconvalescent patients: 1:320 to 1:640

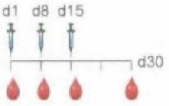
Assessment of Preclinical Safety: GLP Repeat-Dose Toxicity Study in Rats

2-Week repeat dose toxicity study in rats (GLP)

Test sites

- CRL Evreux, France — In-Life
- CureVac, Germany — Dose Formulation Analysis
- VisMederi, Italy — VNT evaluation

Groups	Treatment	ROA	Dose CVnCoV [µg / animal]	Dose Lipids [mg / animal]	Application Volume [ml/animal]	# Animals Main [m/f]	# Animals Recovery [m/f]
1	Control Saline	IM	-	-	0.2	10/10	5/5
2	CVnCoV (low dose)	IM	10	0.25	0.2	10/10	-
3	CVnCoV (mid dose)	IM	40	1.00	0.2	10/10	5/5
4	CVnCoV (high dose)	IM	80	2.00	0.2	10/10	5/5



10 µg, 40 µg, 80 µg

Assessment of Preclinical Safety: Safety profile of CVnCoV in line with CureVac's mRNA Platform

IFNα profile indicates improved reactogenicity profile compared to Rabies vaccine (CV7202)

Acceptable safety profile and consistent with immune stimulation by a vaccine and in line with nonclinical safety profile of CureVac's mRNA platform:

- **Local reaction:**
  - Dose-dependent injection site reaction (inflammation and hemorrhage) and draining lymph nodes (increased lymphoid cellularity) at ≥10µg
  - Injection site reaction considered **adverse** at ≥40µg. Fully resolved at 10µg, and partially resolved at ≥40µg.
- Microscopic findings correlated with increased non-adverse white bood cell (WBC) counts (related mainly to neutrophilia) as well as with increased IFNα and fibrinogen concentrations and with secondary prolongation of coagulation parameters.
- **Adverse**, reversible minimal to moderate hepatocellular apoptosis/necrosis observed in females at ≥ 40 µg and males at 80 µg. Findings in liver correlated with minimal increases in ALT and AST activities in females at 80 µg.
- **No-observed adverse effect level (NOAEL)** determined to be **10 µg**

Overview of Clinical Study Design of CureVac's First-in-Human CVnCoV trial

- Partially blinded, placebo-controlled, dose-escalation study in healthy adults (18-60 years of age)
- Several dose groups of 2µg, 4µg, 6µg, and 8µg with 48 vaccinees and 8 placebo recipients per group; 'sentinel group' vaccination with 12µg started after favorable DSMB review
- Two vaccinations administered by intra-muscular injection on day 1 and day 29
- Sites in Tübingen, Hannover, Munich and Gent
- Participants will be followed for at least one year after the last vaccination
- Study assesses safety and reactogenicity as well as immunogenicity of CVnCoV

		2µg	4µg	6µg	8µg	Total
N	Seronegatives	46	46	46	46	184
N	Seropositives	10	9	5	2	26
Total N	CVnCoV + placebo	56	55	51	48	210

Note: as study is blinded number of subjects receiving placebo is unknown and max. 8 per dose level

Ongoing Phase 1 Results Indicate Acceptable Reactogenicity Profile at Doses up to 8µg

Available data set as of Aug 26th, 2020

Systemic and Local Solicited Events by Dose Level and Dosing Occasion (as % of subjects at each time point)

	Systemic Solicited Events				Local Solicited Events			
	2µg	4µg	6µg	8µg	2µg	4µg	6µg	8µg
1st Dose								
Mild	41%	46%	37%	31%	41%	66%	49%	54%
Moderate	7,1%	24%	33%	35%	3,6%	1,8%	7,8%	17%
Severe	3,6%	9,1%	5,9%	15%	0%	1,8%	2,0%	2,1%
N	56	55	51	48	56	55	51	48
2nd Dose								
Mild	29%	59%	28%	40%	44%	62%	50%	67%
Moderate	7,4%	20%	25%	27%	0,0%	4,4%	6,3%	0%
Severe	1,9%	8,9%	16%	20%	0,0%	0,0%	0,0%	0%
N	54	45	31	15	54	45	31	15

- Grade 1 to Grade 3 reactions appear to increase with dose
- Most Grade 3 events resolved to lower Grades after one day (others remained at Grade 3 for 2 days)
- Lower reactogenicity in 41-60 year old adults (yoa) vs 18-40 yoa (data not shown)

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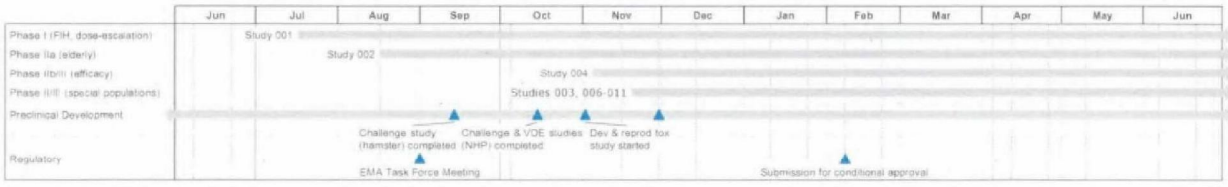
CureVac's SARS-CoV-2 Vaccine Program - CVnCoV

- Interaction with EMA task force (ETF) to define path to approval:
- Briefing document validated and review started on 18-Aug – Response by 08-10 Sep by ETF
- Approval by National Authorities received for 002 trial in Panama and Peru: study in older adults
- Scientific advices scheduled for
- 001: inclusion of older adults in EU: request sent to Belgian FAMHP
- 003: study in immunocompromised subjects: request sent to Belgian FAMHP



Preclinical data supporting full development and approval

Overall preclinical program part of EMA task force briefing document (feedback expected 10-Sep) - Further details to be aligned in upcoming Health Authority interactions

Challenge/efficacy studies: aligned approach with CEPI and external expert groups

- Aim: Assess protective efficacy and define risk of Vaccine Dependent Enhancement (VDE) of disease
- Animal models:
  - Non-human primate – study ongoing at Public Health England (CEPI-funded)
  - Hamster - 2 studies ongoing at Viroclinics, NL

Toxicology:

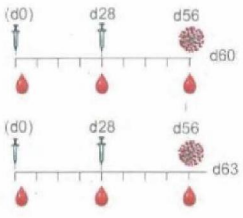
- Based on current regulatory guidance no further repeat-dose study deemed necessary
- Developmental and Reproductive Toxicity (DART):
  - Final GMP material to be used – study scheduled at CRL
  - Start planned in Nov-2020 upon availability of GMP material

- Data on challenge/protection and VDE planned to be included as part of the submission for start of Phase 2b/3 (004 trial; Oct-2020)
- Data on challenge/protection, VDE and DART planned to be included as part of submission package for conditional approval (Q1/2021)

Challenge study in hamsters

Challenge and Evaluation of VDE in Hamsters:

- mRNA and vaccination: Test different doses and protection upon 2 vs. 1 vaccination
- Controls: Alum adj. S protein, FI virus, Live virus infection
- Assessed parameters:
  - Protection from challenge infection: Viral load in lungs and upper respiratory tract, affected lung tissue
  - Serological responses: ELISA and virus neutralizing titers
  - Signs of enhanced disease: Histological analyses: lung, nasal turbinate, gastrointestinal tract brain, heart, liver preserved
    Cytokines (TBD), i.e. IL5, IL4, IL13
- Studies
  1. Active immunization study 1: Termination **d4** post challenge
     → High levels of virus in the lungs
     → low level of alveolitis expected
  2. Active immunization study 2: Termination **d7** post challenge
     → Low levels of virus in the lungs
     → High level of alveolitis expected



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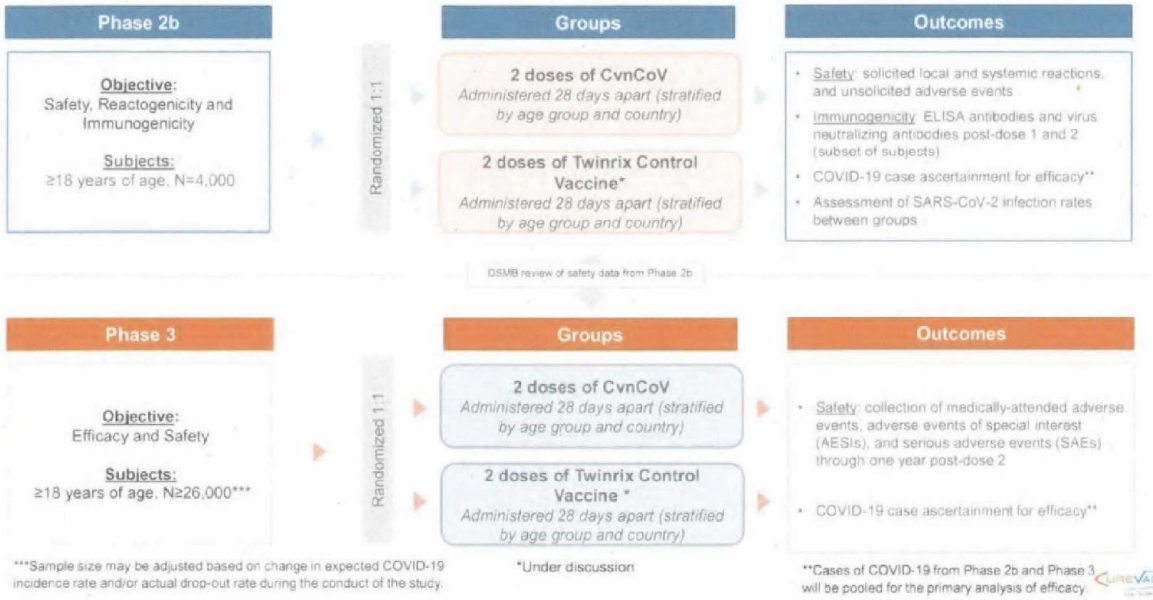
Study CV-NCOV-004: Phase 2b/3 Efficacy Study



***Sample size may be adjusted based on change in expected COVID-19 incidence rate and/or actual drop-out rate during the conduct of the study.

*Under discussion

**Cases of COVID-19 from Phase 2b and Phase 3 will be pooled for the primary analysis of efficacy.

CVnCoV Presentations Upon Approval

- The injected volume for one dose is expected to be 0.4 ml (conditional approval) and 0.5ml (full approval)
- Concentrated mRNA vials and diluent vials will be packed separately

Note: Current Phase 1 storage is at -80°C; stability studies for commercial product are ongoing to support shelf-life at 2-8°C.
1 month stability at 5°C available; 6 months available by November 2020

CureVac will Seek EMA Conditional Approval followed by Full Registration

Conditional Approval

- Basis for conditional approval will be data from studies 001, 002, 004 (Phase 2b part) and 005
- CureVac will conduct rolling submission to support conditional approval
- Robust preclinical and CMC data package will be provided in the initial submission
- Clinical data from all ongoing studies will be submitted (to achieve conditional approval requirements pending EMA scientific advice)
- **Complete submission in 1Q 21**

Full Registration

- When sufficient clinical and manufacturing data are available, CureVac will seek full approval
- Full registration submission will be based on data from 001, 002, 004 (Phase 2b/3) and 005 studies
- Case driven efficacy
- Submission package will include additional safety data from 003 study and preliminary durability of response from 001 and 002 studies
- Post-approval commitments anticipated
- **Complete submission by end of 3Q 21**

EMA Scientific Advice has been requested and is anticipated by 10 September

CUREVAC
the RNA people®

CureVac AG
Friedrich-Miescher-Strasse 15
72076 Tübingen, Germany
T 5.1.2e
www.curevac.com

RNActive® RNArt® RNAdjuvant® PureMessenger® RNAntigen® RNAntibody® RNAnimal® CVCM® The RNA Printer®

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10.2.

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2/1.2 Capacity for the development of a successful Covid-19 vaccine

CureVac has obtained proof of concept for its innovative mRNA platform in prior preclinical and clinical stage projects. In addition, promising preclinical safety and immunogenicity results in animal models supported progression of CureVac's CVnCoV vaccine candidate into an ongoing Phase 1 clinical study which is also generating encouraging tolerability and immunological results.

Based on the above CureVac confirms that it has very good capacity to develop a successful and safe vaccine.

Evidence:

- Scientific and technical presentation (see attached)

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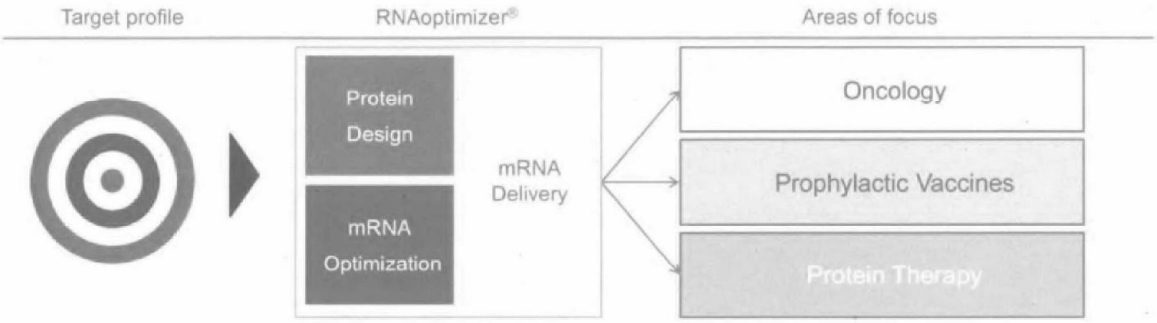
RNAoptimizer® Creates Unique, IP-protected Product Candidates

1 Identification of a target expression profile for each mRNA product candidate

2 RNAoptimizer® provides optimal mRNA solutions for each target indication

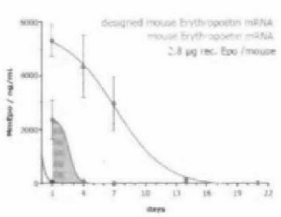
3 The optimization process allows us to pursue new and exclusive IP protection for each product candidate across our focus areas and proprietary technologies



Protein Design: Enables the Optimization of Specific Properties of the Encoded Protein

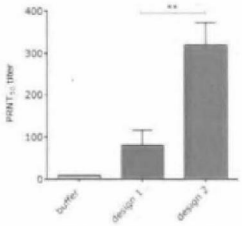
- Ability to modify amino acid sequence to optimize protein properties including half-life, stabilization of tertiary structure, oligomerization, secretion and immunogenicity
- Bespoke and multi-factorial to support distinct functions and requirements of the specific target protein

Extended half-life of secreted protein



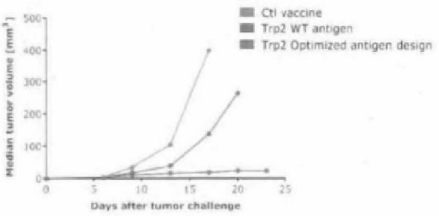
Relevant serum titers of functional Epo and different pharmacokinetic profiles

Oligomerization



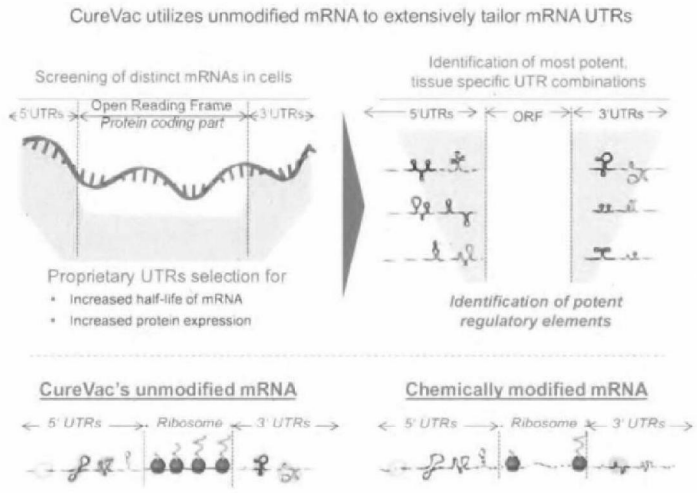
Higher induction of neutralizing antibodies demonstrated via optimized mRNA

Modified immunogenicity

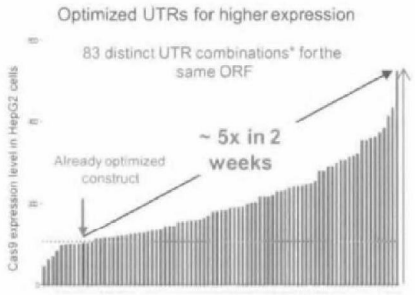


Tumor growth inhibited in murine melanoma model

mRNA Optimization: Optimizes *Unmodified* mRNA to Enhance Protein Expression and Stability

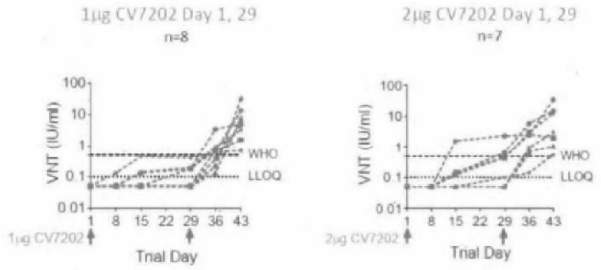


- mRNA optimization process designed to generate the most efficacious mRNA by optimizing translation, stability and immunogenicity
- Ability to optimize six elements of mRNA including 5' cap, 5' UTR, ORF, 3' UTR, and 3' poly-A tail and 3' end



CureVac's Rabies Vaccine CV7202 Induces Protective Antibody Titers at Dose Levels of 1µg and 2µg

CV7202 –Rabies Vaccine –1µg dose x 2 (n=8); 2µg dose x 2 (n=7)

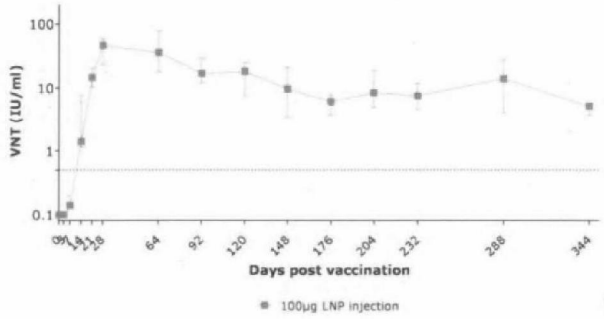


Preliminary data
Values <LLOQ are shown as half LLOQ

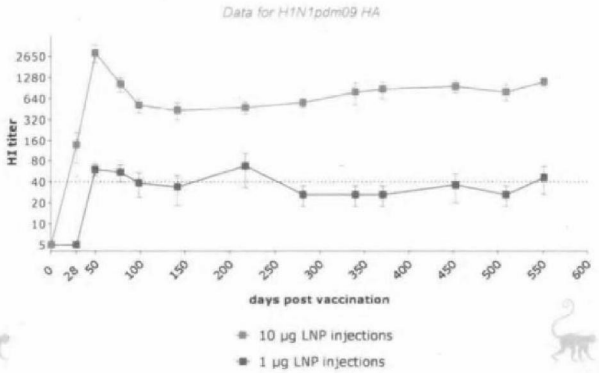
- All volunteers were protected after the 2nd administration of 1µg or 2µg rabies vaccine
- Detectable VNTs as early as 8 days after 1 administration in some subjects
- After two IM doses of 1µg or 2µg, 28 days apart, all subjects with available data had VNTs above the ≥0.5IU/mL WHO recommended antibody level, 14 days after Dose 2 (Day 43)
- Vaccinations were well tolerated
- No SAEs reported
- Durability of response: currently available follow-up at 6 month show stable antibody titers

Long Durability of Response Demonstrated at All Doses Across Different Vaccines

Rabies mRNA vaccine induced high titers of virus-neutralizing antibodies (VNT) after a single IM injection



mRNA flu vaccine demonstrated strong and durable immunogenicity in non-human primates (NHP)



CUREVAC

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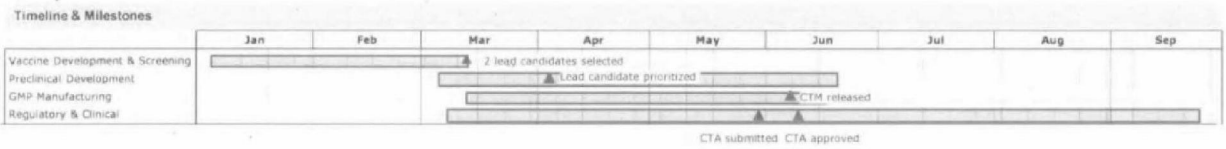
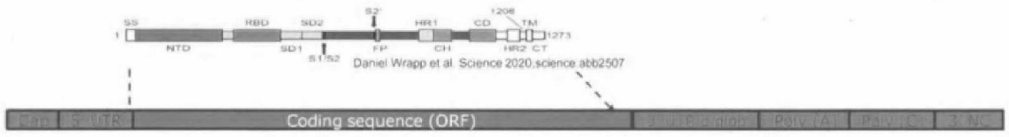
CureVac's SARS-CoV-2 Vaccine Program – CVnCoV Development Status

- Clinical candidate CVnCoV selected based on biological properties and manufacturability
- Characterization of immunogenicity and safety evaluated in vitro and in vivo (mice and rats)
- Manufacturing in new GMP III facility (Tuebingen, Germany) and new fill-and-finish at CMO (Polymun, Austria)
- Approval of First-in-Human trial (CV-NCOV-001) by German PEI and Belgian FAMHP – 1st subject vaccinated on June 19th
- Interaction with EMA task force (ETF) to define path to approval:
  - Briefing document submitted on 14-Aug – Response expected by 08-10 Sep by ETF



CVnCoV Encodes the Full-Length Spike (S) Protein as Antigen



	R number	ORF	Codon usage
CVnCoV Clinical Candidate	R9515	Full length stabilized S protein	CureVac proprietary algorithm

Characteristics of the Coronavirus S protein: Trimer forming glycoprotein on the viral surface
Parallel to previously developed antigens at CureVac (influenza HA, rabies G, RSV F, HIV-1 Env)

Employing S protein as an antigen: Only significant target for neutralizing antibodies for Coronaviruses
→ S protein has been widely used in the context of SARS and MERS vaccine candidates

Stabilized version published for MERS and SARS: designed to prevent the transition from the pre-fusion to post-fusion states → Candidate constructs were designed to increase the induction of VNT over binding antibodies

Characterization of mRNA-Induced Immune Responses

in vitro characterization of IFNα induction

- Tested doses: Mouse Serum: 4µg, 1µg, 0.25µg; Human PBMCs: 5µg/1x10^6 cell

in vivo characterization of humoral and cellular responses

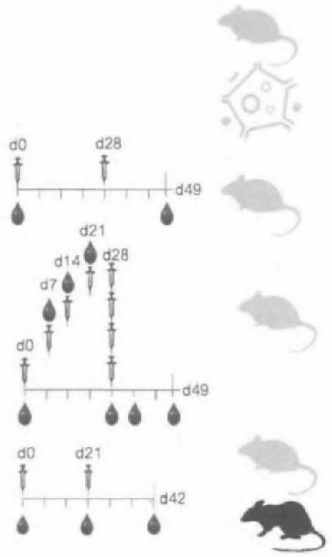
- Tested dose: **2 µg**

Impact of vaccination schedule

- Tested dose: **2 µg**
- Vaccination schedules: time interval between 1st and 2nd vaccination: **4, 3, 2 or 1 week**

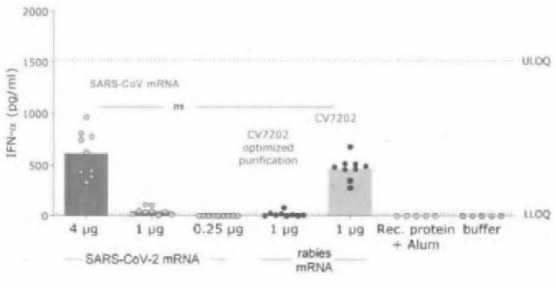
Assessment of dose range

- Mice - tested dose range: **0.25 µg, 1 µg, 4 µg**
- Rats - tested dose range: **0.5µg, 2µg, 10µg, 20µg, 80µg**

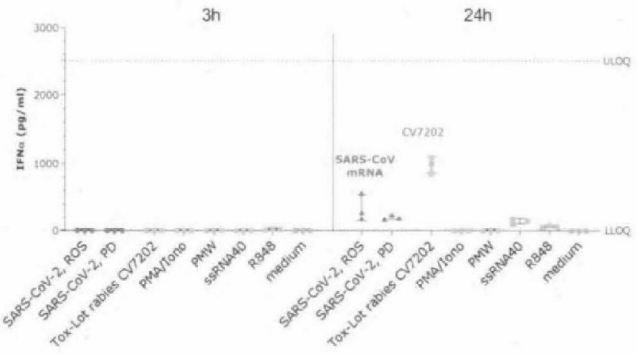


Characterization of IFNα induction: CVnCoV induces lower levels of IFNα compared to CV7202*

IFNα induction mouse serum 14h p.i.



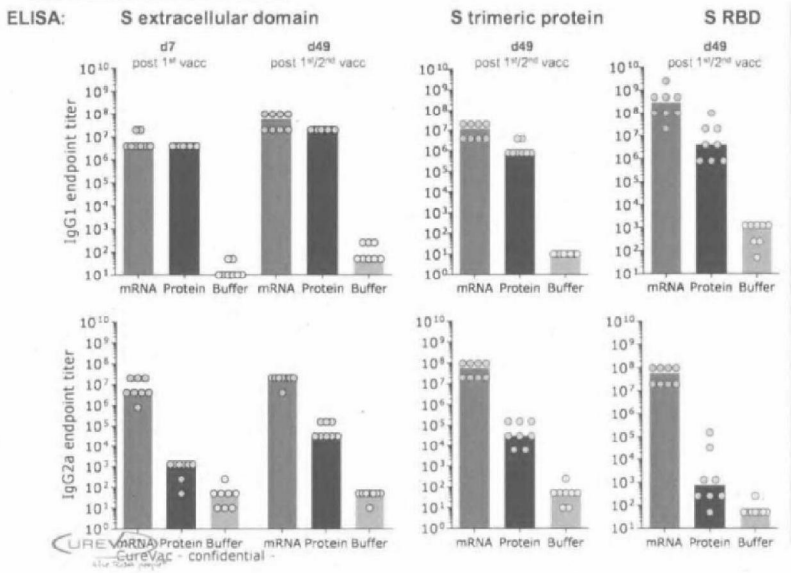
IFNα induction in hPBMCs

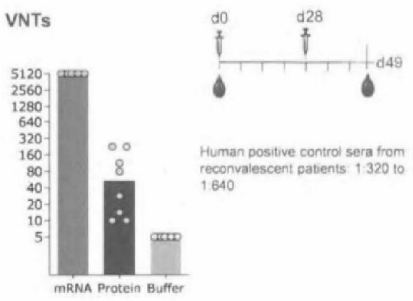


- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Evaluation: IFNα levels via ELISA

*CV7202 refers to the material used in the Rabies clinical trial 104

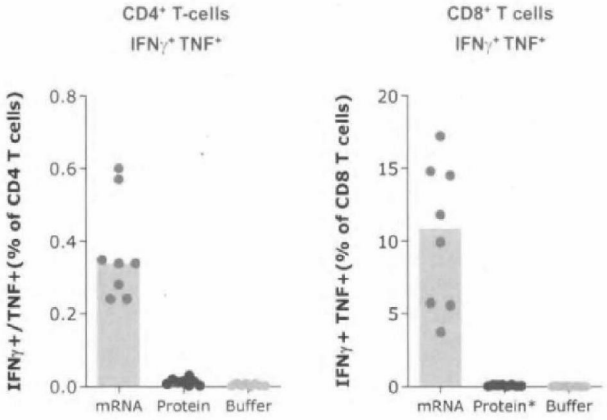
Characterization of humoral and cellular responses: CVnCoV induces antibody responses with strong binding to the RBD

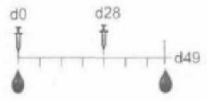




- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Evaluation:
  - ELISA: coating with SARS-CoV-2 S extracellular domain, trimeric protein or RBD (receptor binding domain)
  - VNTs: Cytopathic effect (CPE) based microneutralization at VisMederi

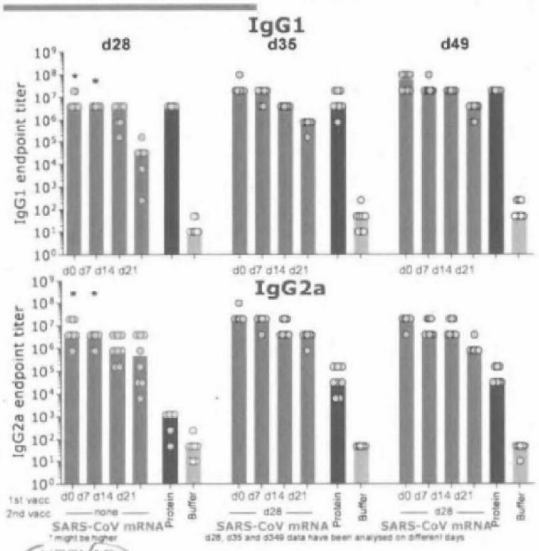
Characterization of humoral and cellular responses: CVnCoV induces high levels of double positive T-cell responses

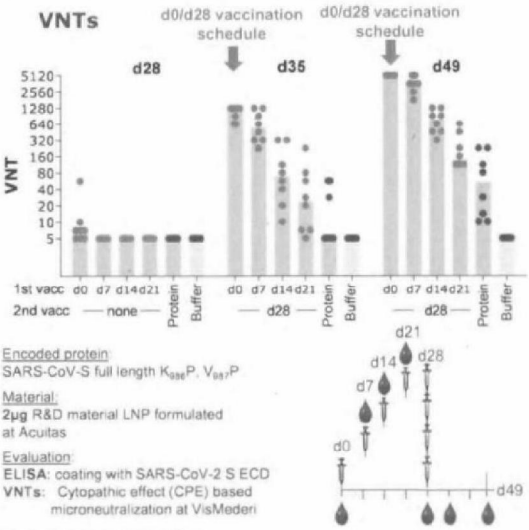




- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Evaluation: ICS stimulated with S full length library 11 mers 15 overlapping

Impact of vaccination schedule:
A 4-week vaccination schedule provides the best immune response

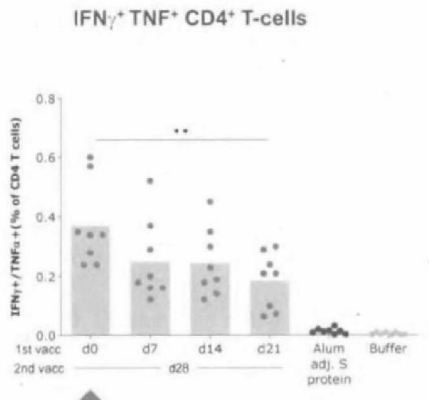


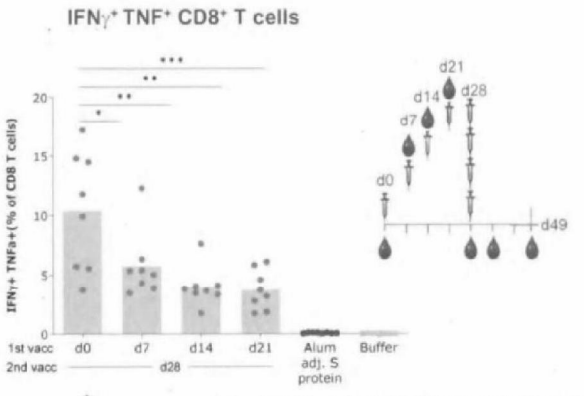


- Encoded protein:
  SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Material:
  2µg R&D material LNP formulated at Acuitas
- Evaluation:
  ELISA: coating with SARS-CoV-2 S ECD
  VNTs: Cytopathic effect (CPE) based microneutralization at VisMederi

Human positive control sera from reconvalescent patients: 1:320 to 1:640

Impact of vaccination schedule:
T cell responses in mice increase with longer vaccination schedule

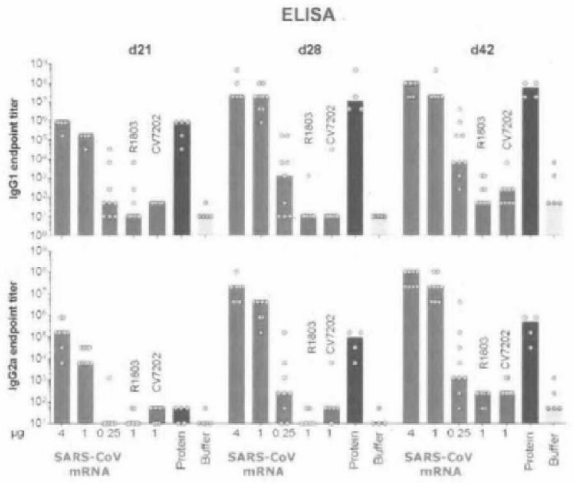


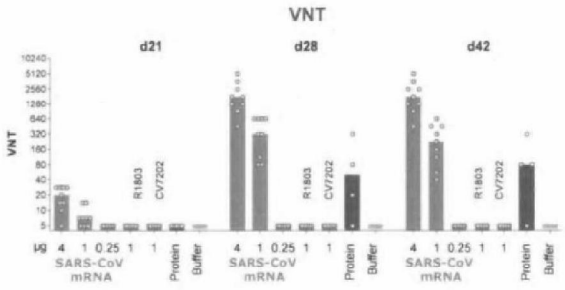


- Encoded protein: SARS-CoV-S full length $K_{986}P$, $V_{987}P$
- Material: **2 µg** R&D material LNP formulated at Acuitas
- Evaluation: ICS stimulated with S full length library of 15-mers overlapping by 11

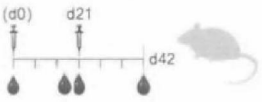
CureVac - confidential -

Assessment of dose range – mice:
CVnCoV induces robust immune responses at 1 µg and above

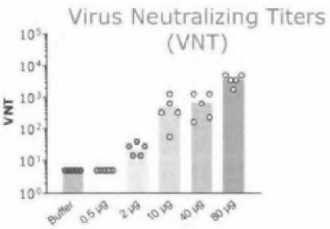


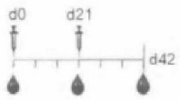


- Encoded protein: SARS-CoV-2 S full length $K_{986}P$, $V_{987}P$
- Material: PD material LNP formulated at Polymun
- Evaluation
  - **ELISA:** coating with SARS-CoV-2 S ECD
  - **VNTs:** Cytopathic effect (CPE) based microneutralization at VisMederi
  - Human positive control sera from reconvalescent patients: 1:320 to 1:640

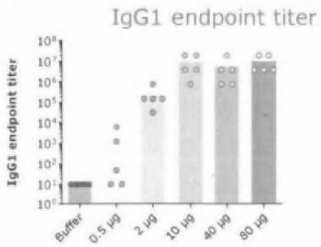


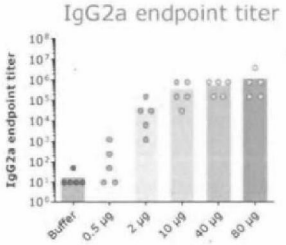
Assessment of dose range – rats:
CVnCoV induces dose-dependent immune responses





- Encoded protein: SARS-CoV-2 S full length $K_{986}P$, $V_{987}P$
- Evaluation:
  - **ELISA:** coating with SARS-CoV-2 S ECD
  - **VNTs:** Cytopathic effect (CPE) based micro-neutralization at VisMederi, Italy





Human positive control sera from reconvalescent patients: 1:320 to 1:640

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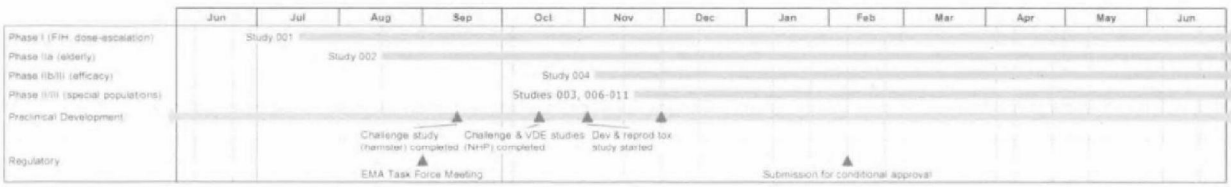
CureVac's SARS-CoV-2 Vaccine Program - CVnCoV

- Interaction with EMA task force (ETF) to define path to approval:
- Briefing document validated and review started on 18-Aug – Response by 08-10 Sep by ETF
- Approval by National Authorities received for 002 trial in Panama and Peru: study in older adults
- Scientific advices scheduled for
- 001: inclusion of older adults in EU: request sent to Belgian FAMHP
- 003: study in immunocompromised subjects: request sent to Belgian FAMHP



Preclinical data supporting full development and approval

Overall preclinical program part of EMA task force briefing document (feedback expected 10-Sep) - Further details to be aligned in upcoming Health Authority interactions

Challenge/efficacy studies: aligned approach with CEPI and external expert groups

- Aim: Assess protective efficacy and define risk of Vaccine Dependent Enhancement (VDE) of disease
- Animal models:
  - Non-human primate – study ongoing at Public Health England (CEPI-funded)
  - Hamster - 2 studies ongoing at Viroclinics, NL

Toxicology:

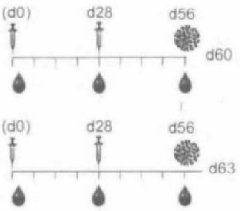
- Based on current regulatory guidance no further repeat-dose study deemed necessary
- Developmental and Reproductive Toxicity (DART):
  - Final GMP material to be used – study scheduled at CRL
  - Start planned in Nov-2020 upon availability of GMP material

- Data on challenge/protection and VDE planned to be included as part of the submission for start of Phase 2b/3 (004 trial; Oct-2020)
- Data on challenge/protection, VDE and DART planned to be included as part of submission package for conditional approval (Q1/2021)

Challenge study in hamsters

Challenge and Evaluation of VDE in Hamsters:

- mRNA and vaccination: Test different doses and protection upon 2 vs. 1 vaccination
- Controls: Alum adj. S protein, FI virus, Live virus infection
- Assessed parameters:
  - Protection from challenge infection: Viral load in lungs and upper respiratory tract, affected lung tissue
  - Serological responses: ELISA and virus neutralizing titers
  - Signs of enhanced disease: Histological analyses: lung, nasal turbinate, gastrointestinal tract brain, heart, liver preserved
    Cytokines (TBD), i.e. IL5, IL4, IL13
- Studies
  1. Active immunization study 1: Termination **d4** post challenge
     → High levels of virus in the lungs
     → low level of alveolitis expected
  2. Active immunization study 2: Termination **d7** post challenge
     → Low levels of virus in the lungs
     → High level of alveolitis expected



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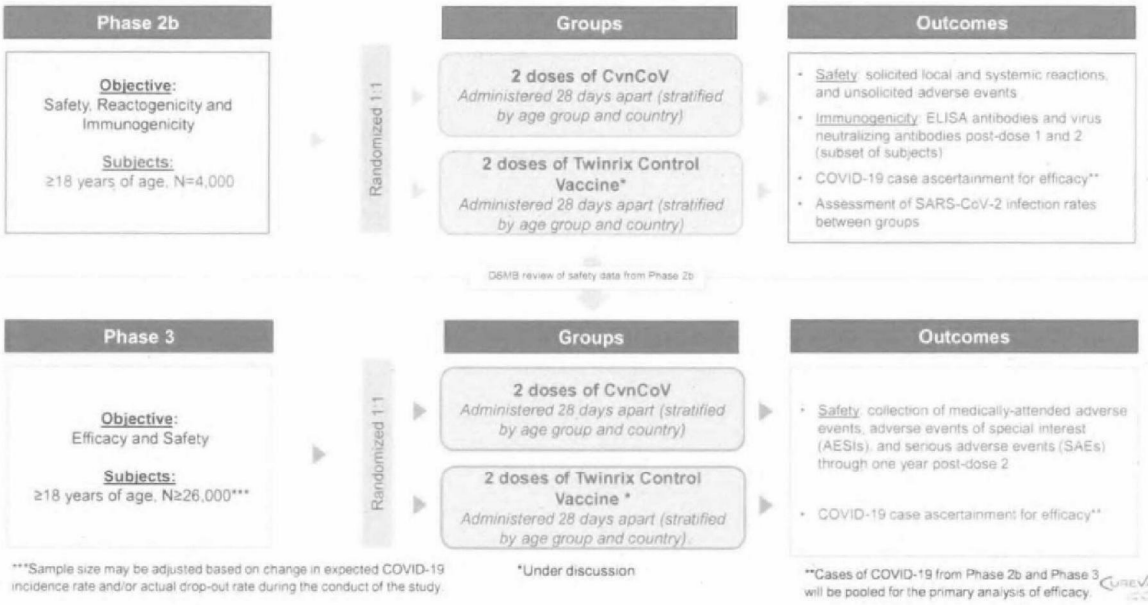
Study CV-NCOV-004: Phase 2b/3 Efficacy Study

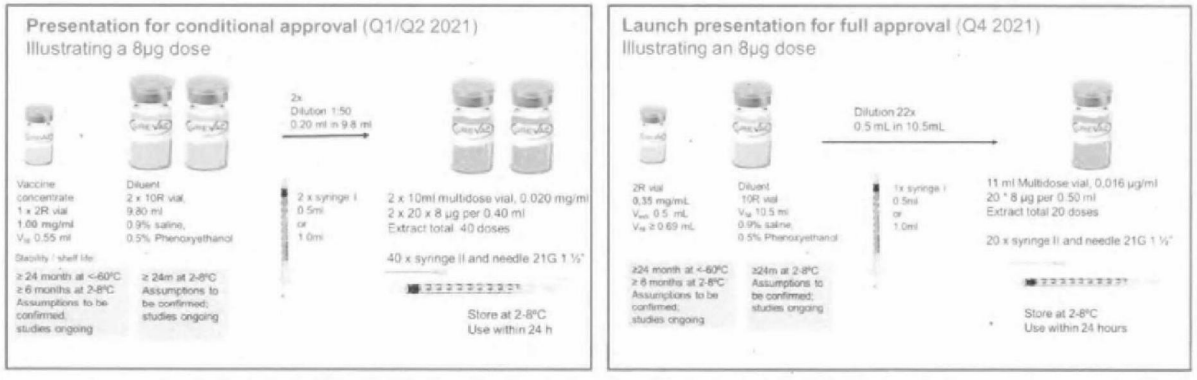


***Sample size may be adjusted based on change in expected COVID-19 incidence rate and/or actual drop-out rate during the conduct of the study

*Under discussion

**Cases of COVID-19 from Phase 2b and Phase 3 will be pooled for the primary analysis of efficacy.

CVnCoV Presentations Upon Approval



- The injected volume for one dose is expected to be 0.4 ml (conditional approval) and 0.5ml (full approval)
- Concentrated mRNA vials and diluent vials will be packed separately

Note: Current Phase 1 storage is at -80°C; stability studies for commercial product are ongoing to support shelf-life at 2-8°C.
1 month stability at°5°C available; 6 months available by November 2020

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CureVac will Seek EMA Conditional Approval followed by Full Registration

Conditional Approval

- Basis for conditional approval will be data from studies 001, 002, 004 (Phase 2b part) and 005
- CureVac will conduct rolling submission to support conditional approval
- Robust preclinical and CMC data package will be provided in the initial submission
- Clinical data from all ongoing studies will be submitted (to achieve conditional approval requirements pending EMA scientific advice)
- **Complete submission in 1Q 21**

Full Registration

- When sufficient clinical and manufacturing data are available, CureVac will seek full approval
- Full registration submission will be based on data from 001, 002, 004 (Phase 2b/3) and 005 studies
- Case driven efficacy
- Submission package will include additional safety data from 003 study and preliminary durability of response from 001 and 002 studies
- Post-approval commitments anticipated
- **Complete submission by end of 3Q 21**

EMA Scientific Advice has been requested and is anticipated by 10 September

CUREVAC
the RNA people®

CureVac AG
Friedrich-Miescher-Strasse 15
72076 Tübingen, Germany
T [redacted] 5.1.2e
www.curevac.com

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