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2 - 5

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Pagina's zijn verwijderd 620375

7 - 8

5.1.1c

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10.5.

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2/1.5 Speed of delivery of supplies

Unless we misunderstood the description, because the orders of the Member States should be fixed upon signature of the EU APA contract (through the Specific Contracts in the appendix) in the coming weeks, and because deliveries would be staged from Q1 2021 to Q1 2022, this award criteria does not seem relevant in this context.

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10.6.

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2/1.6 Intention to seek EU marketing authorization

The core regulatory pathway chosen by CureVac is EMA marketing authorization. This will be followed by additional regulatory dossier submissions as required in other countries which are ordering vaccines from CureVac. This process is already on-going and CureVac is working towards its plan while awaiting feedback from EMA which is expected in September 2020.

Based on the above CureVac confirms that it has engaged with EU regulator with the intention to seek future EU marketing authorization at the time of submitting the tender.

Evidence:

- Clinical Trial Approval for Belgium and Germany for Phase1 currently ongoing was granted in June 2020 (see attached)
- EMA briefing document submitted to COVID-19 EMA task force (ETF) that outlines path to conditional approval followed by MAA. Document focuses on preclinical and clinical topics and was submitted on 14-Aug and validated by EMA for review on 18-Aug. A second ETF briefing document and request for feedback will be submitted by September 2020 with focus on CMC and manufacturing topics. (See attached)

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Federal Institute for Vaccines and Biomedicines

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CureVac AG

5.1.2e

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EudraCT-Nr. 2020-001286-36
Vorlage-Nr.: 4121/01
Bearbeiter/in: 5.1.2e
Referatsleiter klin. Prüfungen/Ref. S5
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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

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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

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.

Version 1

CHMP/COVID-ETF Scientific Advice
Briefing Document

Invented Name:	CVnCoV, CV07050101
Drug substance:	R9515
Pharmaco-therapeutic group:	Immunisations
Intended indication(s):	COVID-19 immunisation
Applicant:	CureVac AG
Version	1.0
Date:	17/08/2020

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

ADE	antibody-dependent enhancement
ADEM	acute disseminated encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
ALUM	Aluminium sulfate/phosphate
CEM	cohort event monitoring
CEPI	Coalition for Epidemic Preparedness Innovations
CMC	chemistry, manufacturing, and control
CMI	cell-mediated immunity
CoC	certificate of conformity
CPM	CovidPreventMainz
CSR	clinical study report
CMO	contract manufacturing organization
CT	CAT Scan
CTM	clinical trial material
CV	CureVac
CV07050101	CureVac investigational COVID-19 vaccine
CV7202	CureVac's investigational rabies vaccine
CVnCoV	CureVac's investigational COVID-19 vaccine
DAD	diode array detector
DART	developmental and reproductive toxicology
DSMB	data and safety monitoring board
dLN	draining lymph node
DSMB	data safety monitoring board
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
EFD	embryo-foetal development
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FEED	fertility and early embryo development

FIH	first-in-human
GBS	Guillain Barré syndrome
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMT	geometric mean titre
HCW	healthcare worker
HIV	human immunodeficiency virus
hPBMC	human peripheral blood mononuclear cell
HPLC	high-performance liquid chromatography
HSL	histone stem loop sequence
IB	Investigator's Brochure
IC	immunocompromised
IFN	interferon
ILI	influenza-like illness
IM	intramuscular
IMP	investigational medicinal product
IPC	in-process control
ISO	International Organization for Standardization
IVT	*in vitro* translation
LAL	Limulus amebocyte lysate
LNP	lipid nanoparticle
LOD	limit of detection
LTFU	long term follow up
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MHC	major histocompatibility complex
mRNA	messenger ribonucleic acid
NHP	non-human primate
NOAEL	no observed adverse effect level
ORF	open reading frame
PAES	post-authorisation efficacy study
PASS	post-authorisation safety study

PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
pDNA	plasmid DNA
PEI	Paul-Ehrlich-Institute
pIMD	potential immune-mediated disease
PIP	paediatric investigation plan
PMID	PubMed reference number assigned by NIH National Library of Medicine
PPND	pre- and postnatal development
PV	pharmacovigilance
PVP	Pharmacovigilance Plan
qPCR	quantitative polymerase chain reaction
QR	Quick Response code or two-dimensional bar code
QW	once weekly
R (10R, 2R)	R=mL
RABV-G	rabies virus glycoprotein
RCB	research cell bank
RMM	risk minimisation measure
RMP	Risk Management Plan
RNA	ribonucleic acid
RP-HPLC	reverse phase high-performance liquid chromatography
RSV	respiratory syncytial virus
S	spike
SA	scientific advice
SAE	serious adverse event
SARI	severe acute respiratory illness
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCS	self-controlled case-series
SmPC	Summary of Product Characteristics
SPEAC	Safety Platform for Emergency vACcines
TBD	to be decided

TEAA	triethylammonium acetate
Th1, Th2	T-helper cell type 1, T-helper cell type 2
TLR7	toll-like receptor 7 stimulation
TP	time point
UTR	untranslated region
VDE	vaccine-dependent disease enhancement
VE	vaccine effectiveness
VEP	vaccine effectiveness for progression
VNT	virus neutralisation test
WB	Western Blot
WHO	World Health Organization
YOA	years of age

Pagina's zijn verwijderd 620375

24 - 24

5.1.1c

As a result of mRNA translation from the vaccine mRNA, antigen presentation and immune stimulation, long-lived adaptive immune responses against the encoded antigens are induced (Lutz et al, 2017).

Possible Risks and Adverse Drug Reactions

The LNP-formulated RNActive® platform was used with CureVac's rabies vaccine (CV7202) at 1-5 µg mRNA in a first-in-human study (CV-7202-104, EUDRACT No. 2017-002856-10). Based on previous clinical experience with CV7202 and CVnCoV (either 2 µg, 4 µg, 6 µg, 8 µg mRNA), local reactions (pain, redness, itching, and swelling at the injection site) and systemic adverse events (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhoea) occurred and resolved within 24 hours after the vaccination. After administration of CV7202, in addition to the systemic AEs described above, a few subjects experienced decreased appetite, night sweats, and tachycardia (see Annex 1).

As for all vaccines, the occurrence of allergic/anaphylactic reactions cannot be excluded and emergency equipment for the treatment of such reactions must be available at the trial site. These events are unexpected and constitute a potential important medical risk. So far, no allergic/anaphylactic reactions have been observed in the completed and ongoing clinical trials after repeated administration of protamine-formulated RNActive® vaccines, nor after administration of CV7202 in the CV-7202-104 trial. In study CV-NCOV-001, a case of grade 1 macular rash has been reported after the first vaccination in one participant. This rash was self-limiting. It was assessed as being of an allergic nature by the investigator (allergy to kanamycin is in the study exclusion criteria so this type of allergy is not known to be the case).

During the early stages of manufacture of CVnCoV, kanamycin was used in the plasmid DNA (pDNA) manufacturing process. Although there is no evidence of residual kanamycin in the final IMP, subjects with a previous class I allergic reaction to aminoglycoside antibiotics should be excluded from vaccination with CVnCoV as a measure of precaution.

In an ongoing 14-day repeat-dose toxicity study, rats were administered CVnCoV via IM injection once weekly (total 3 dose administrations), followed by a 14-day non-dosing recovery period. Based on preliminary data from the ongoing repeat-dose study, once weekly IM administration was well tolerated and findings were consistent with an immune response expected of a vaccine.

Developmental toxicity studies have not been conducted with CVnCoV. Preliminary data from a 14-day toxicity study with CVnCoV revealed no test item related gross necropsy findings in the reproductive organs in rats. Data from repeat-dose toxicity studies with CureVac's rabies vaccine CV7202 conducted in rats and rabbits showed that there were no histopathological findings in the reproductive organs. Furthermore, in a biodistribution study conducted in mice with CV7202, there were no toxicologically relevant levels of RNA detected in reproductive organs. Based on these data, teratogenicity risk is considered to be low. However, given that there are no adequate and well-controlled studies of CVnCoV in pregnant women, a risk to the developing baby cannot be excluded at this time. For this reason, inclusion of female subjects of childbearing potential requires use of effective contraceptives one month before the first administration of the test vaccine until 3 months following the last administration.

Quality development

The quality section herein is intended for background for other sections of this document. A future EMA scientific advice (SA) focused on quality aspects is targeted for early 4Q 2020 in order to discuss quality questions and applicant's position pertaining to Phase 2b/3 and proposed conditional marketing authorisation (CMC-focused EMA SA).

The drug substance R9515 is an mRNA encoding the stabilised full-length spike (S) SARS-CoV-2 virus antigen. The mRNA was optimised by CureVac's (CV) proprietary GC enrichment algorithm to optimise protein expression and innate immune stimulation. The GC content is 62.76%.

By design, R9515 incorporates amino acid substitutions (Lysine to Proline at position 986 [K986P] and Valine to Proline at position 987 [V987P]), aimed to stabilise the spike protein in the pre-fusion confirmation. Mutations are based on parallel designs in Middle East respiratory syndrome (MERS) S protein that have been shown to stabilise the pre-fusion conformation of the protein and improve the ratio between binding and neutralising antibody titres (Pallesen et al, 2017).

study demonstrated the induction of binding antibodies against the encoded S protein and produced virus-neutralising antibodies at doses of 1 and 4 µg after 2 vaccinations. Moreover, a positive dose-response relationship and a significant boost effect of the 2nd vaccination was confirmed.

Clinical development

A Phase 1 first-in-human (FIH) study in healthy adults 18 to 60 years of age was initiated in June 2020 in Belgium and Germany (EUDRACT No. 2020-001286-36), with the goal of generating data on the safety, reactogenicity and immunogenicity of CVnCoV at escalating doses. The population will then be expanded in a Phase 2a study to include elderly adult's ≥ 61 years of age as this age group is disproportionally affected by this disease. Scientific advice has been previously received from two national agencies, the German Paul-Ehrlich-Institute (PEI) and the Belgian Federal Agency for Medicines and Health Products (FAMHP) on three occasions: national SA with PEI on 30 Jan 2020, national SA with FAMHP on 19 March 2020, and Joint Scientific Advice PEI and FAMHP on 12 May 2020.

Phase 2b/3 trials are planned to demonstrate the efficacy of CVnCoV against COVID-19 disease, as well as to generate a large-scale, comprehensive safety database. A potential conditional marketing authorisation, based on interim datasets, will be sought to address the global unmet medical need of the pandemic provided the benefit-risk balance of CVnCoV is positive and with the understanding that a comprehensive dataset will be submitted at a later date for a standard marketing authorisation.

In order to pursue a potential conditional marketing authorisation as soon as possible, conduct of the pivotal Phase 2b/3 efficacy study and proposed conditional authorisation are envisioned with a refrigerated concentrated vaccine drug product that will need to be diluted ~1:100 in diluent prior to administration. Should the interim clinical data be favourable, the applicant considers that the immediate availability of CVnCoV on the market (conditional marketing authorisation for use in mass vaccination campaigns) outweighs the risks of waiting for the full clinical dataset availability, which would follow approximately six months later.

CureVac's mRNA vaccines containing the LNP delivery system, particularly in the currently ongoing rabies programme (CV7202), have been shown to induce high magnitude and durable antibody titres in subjects, even at doses as low as 1 µg. Furthermore, SARS-CoV-2 specific immune responses including binding and virus neutralisation antibodies as well antigen-specific T-cells to the spike protein have been induced in a mouse model. Since in a pandemic setting providing protection with a low dose vaccine is important to be able to vaccinate large parts of the population at risk, the same technology is being applied for the SARS-CoV-2 candidate vaccine CVnCoV.

The Phase 2b/3 pivotal trial, specifically the Phase 2b portion, was designed to provide detailed safety, reactogenicity and immunogenicity data in support of the proposed conditional marketing authorisation. For the submission of the conditional authorisation application, COVID-19 case data will be collected, and a preliminary vaccine efficacy estimate will be available, in support of the benefit of CVnCoV. The Phase 2b/3 study would continue after conditional marketing authorisation in order to provide the full comprehensive dataset confirming the efficacy and safety of CVnCoV. A Rolling Review procedure is proposed to allow EMA to continuously assess the data as they become available.

A Paediatric Investigational Plan (PIP) will be submitted once the Phase 2b/3 study is underway. It is intended to request a deferral of paediatric studies until the data for the conditional marketing authorisation would be available. Thus, the first paediatric study would be initiated, per the proposed PIP, after safety, reactogenicity, immunogenicity and potentially preliminary efficacy data, for what is planned to be used to obtain conditional marketing authorisation, are collected in adults.

Further details on the clinical strategy are described in the applicant's position with the corresponding clinical questions.

Regulatory status

PEI CTA Approval Letter for clinical Phase 1 trial, 16 June 2020
FAMHP CTA Approval Letter for clinical Phase 1 trial, 17 June 2020
The product is not marketed in any region.

A Conditional Marketing Authorisation is sought in the EU in the first half of 2021.

Rationale for seeking advice

This scientific advice is intended to receive advice on the following:

1. Acceptability of multi-dose vial presentation with preservative
2. Acceptability of the proposed non-clinical, toxicology and clinical data package for initiation of Phase 3.
3. Acceptability of the proposed non-clinical, toxicology and clinical data package for a Conditional Marketing Authorisation for prevention of COVID-19 disease in persons 18 years of age and above.
4. Acceptability of proposed clinical data for conversion from Conditional Marketing Authorisation into a standard Market Authorisation for persons 18 years of age and above.
5. Acceptability of the planned Risk Management Strategy: namely, on whether the Summary of Safety Concerns is complete and correct, and on whether the planned Pharmacovigilance Plan (PVP) and the planned RMMs are suitable.
6. Acceptability for deferral of paediatric studies until sufficient safety, reactogenicity and (preliminary) efficacy data are available in adults.

II. Questions and Applicant's Positions

A. Questions on Multi-Dose Vial Presentation

Question 1

Does the EMA agree to the product presentation intended for Conditional Marketing Authorisation?

Question 2

Does EMA agree with the proposed containers, closures and syringes for Phase 2b/3 and for marketed vaccine after a Conditional Marketing Authorisation?

Question 3

Does EMA agree with the proposed Summary of Product Characteristics (SmPC) Section 6 (Pharmaceutical Particulars) in support of a Conditional Marketing Authorisation for mass vaccination campaigns?

Applicant's Position Questions 1-3

A multi-dose vial presentation is planned for use in Phase 2b/3, for the proposed conditional marketing authorisation application and launch following conditional market authorisation launch. The vaccine will contain a preservative, 2-phenoxyethanol.

Proposed language/artwork for SmPC associated with presentation is shown in Figure 3.

Containers and syringes proposed for Phase 2b/3 and for Conditional Marketing Authorisation Application are summarised in Table 1. The manufacturers of the containers and syringes are provided in Table 3.

Drug Product container compatibility testing / in-use stability testing summary are summarised in Table 2.

Brief description of handling which is to be done by healthcare providers

Using the syringe for transfer of the drug product, a defined volume of drug product will be transferred from the 2-mL drug product vial (ISO 2R) into the dilution vial (ISO 10R). The final dilution factor and final volumes are to be set after definition of the dose. The current plan is to transfer 0.1 mL drug product into the dilution vial using a 1-mL syringe, or more optimally a smaller volume syringe e.g. 0.5-mL, if available, given pandemic related supply chain shortages.

After mixing the dilution vial, by inversion, multiple doses can be taken from this vial, each dose using the syringe for injection, for vaccine administration. The in-use holding times of dilution vial (ISO 10R) containing the diluted drug product and of the syringe for injection loaded with diluted drug product will be determined and specified.

Pagina's zijn verwijderd 620375

30 - 33

5.1.1c

The materials for the in-use stability will be the same as those used in Phase 2b/3 and for launch (see Table 3). This includes 1-mL syringes (for dilution) and 1-mL syringe (for administration). Syringes, 0.5 mL, are also being considered to increase accuracy, predicated on supply chain availability. The vaccine will come with mixing vials filled with sterile preservative containing saline and syringes as a sterile ready-to-use kit. The 10-mL vial filled with 9.9 mL of sterile saline diluent is sealed with 20 mm bromobutyl or chlorobutyl rubber stopper and crimped with a 20 mm aluminum seal fitted flip-off cap. All product-contacting materials are pharmaceutical-grade, suitable for packaging sterile liquid products, and comply with relevant pharmaceutical requirements.

Table 3: Container Closure Description for the In-use Stability Study

Component	Description	Example Manufacturer
Mixing vial (Ready-to-use kit)	Medical device class 1s, CE 72373	Adelphi Tubes Ltd
	Aseptic processing	BAG Health Care GmbH
• Vial	10 mL, ISO 10R glass vial type I	Schott AG
• Rubber stopper	20 mm bromobutyl or chlorobutyl fluorotec coated	West Pharmaceutical Services, Inc.
• Flip-off seal	20 mm aluminium flip-off cap	West Pharmaceutical Services, Inc.
Sterile single-use syringes		
• 1 mL (or 1 mL) syringe for extraction of IMP from 2R vial	Barrel: TBD Plunger rod: TBD Rubber piston: no free lubricant, x gauge needle	BBraun
• 1 mL syringe for IM administration	Barrel: polypropylene Plunger rod: polystyrene Rubber piston with double sealing ring: polyisoprene No excess free lubricant, x gauge needle	BBraun

IM: intramuscular; TBD: to be decided

Question 4

Does the EMA agree that the product information and labelling: SmPC, vial label and outer packaging, including the blue-box, will be provided in English while translation in all official languages will be available online?

Applicant's Position

English product information and labelling will be provided to facilitate the fast movement of the medicinal product for mass vaccination conducted by healthcare professionals during COVID-19 pandemic situation with translation in all official languages online and also by QR code. This will help streamline the labelling/packaging process and logistics to address the urgency of the supply of the medicinal product.

Question 5

Does the EMA agree that the obligation to place two safety features on the packaging of CV07050101 in the European Union: a unique identifier (a 2-dimension barcode) and an anti-tampering device, in accordance with Commission Delegated Regulation (EU) 2016/161, is waived for the pandemic situation for CV07050101?

Applicant's Position

Manufacturing and the final fill and finish of the vials requires that the primary label be placed on the vial prior to freezing of the drug product. As product manufacture will be ongoing prior to the initiation of the Phase 3 efficacy study, a stockpile of frozen vials will be completed before label text is finalised. A barcode identifier, if identified sufficiently in advance, will be placed in the primary label along with basic text for the product name, manufacturer, lot number and storage temperature. An anti-tampering device has not been explored at this point and could be difficult to identify and source for the primary packaging being used in the initially manufactured lots. We have engaged external

experts to address these issues in a timely manner; however, we request a waiver that will permit advance production of finished product vials.

B. Questions on Toxico-Pharmacological Development

Question 6

Provided the data are acceptable, does the EMA agree that the available non-clinical data package, including the challenge studies in hamster, combined with available clinical data are sufficient to support initiation of Phase 3?

Question 7

Provided the data are acceptable, does the EMA agree that non-clinical challenge studies in hamster combined with the available clinical are adequate to support Conditional Marketing Authorisation of CV07050101 for prophylactic administration?

Question 8

Provided the data are acceptable, does the EMA agree with the non-clinical strategy to evaluate potential indicators / signals (e.g. cytokines, histopathology, etc.) of enhanced disease in hamster and NHP to assess the risk for vaccine-dependent disease enhancement (VDE), in addition to the clinical data, in support of Conditional Marketing Authorisation of CV07050101?

Applicant's Position Questions 6-8

Protective efficacy of LNP-formulated RNActive® SARS-CoV-2 vaccine will be assessed in challenge infection models in hamsters and NHPs.

Table 4: Overview of ongoing challenge studies

Animal model	Purpose of study	mRNA Vaccination (IM) and schedule	Controls (IM)	Immunogenicity read-outs	Protective efficacy read-outs	Enhanced disease read-outs	Data availability
Syrian hamster 5/group Study 1: female Study 2: male	Assess protection from viral replication in the lungs and protection from lung pathology (study 1)	Vaccination -10 µg d28 -10 µg d0/d28 -2 µg d0/d28 -0.4 µg d0/d28 Challenge: d56 Termination: d4	Neg ctrl: Buffer Pos. ctrl protective efficacy -SARS-CoV infection Pos. ctrl enhanced disease -Alum adj. protein	-Binding antibody titres (ELISA) -Virus neutralising titres (VNTs)	Protection from challenge infection: -Virus in lungs and upper (daily p.c.) and lower respiratory tract (day of termination) -Histopathology in target organs, gross pathology of the lungs	-Determination of ratio binding/neutralising antibody titres - Histopathology in target organs, gross pathology of the lungs -Induction of cytokines in the lungs upon vaccination/challenge	Prior to Phase 3
	Assess protection from lung pathology (study 2)	Vaccination -8 µg d28 -8 µg d0/d28 -2 µg d0/d28 -0.4 µg d0/d28 Challenge: d56 Termination: d7	Neg ctrl: Buffer Pos. ctrl enhanced disease -Alum adj. protein -Formalin and heat inact. virus				Prior to Phase 3
Rhesus macaques 6/group Male/female	Assess protective efficacy and enhanced disease	Vaccination 8 µg d0/d28 -0.5 µg d0/d28 Challenge: d56 Termination: -d6 (2/6) -d7 (2/6) -d8 (2/6)	Neg ctrl: Buffer Pos. ctrl enhanced disease (historic) Formalin inactivated virus	-Binding antibody titres (ELISA) Virus neutralising titres (VNTs)	Protection from challenge infection: -Virus in lungs and upper (d1, d3, d5 p.c.) and lower respiratory tract (day of termination) Histopathology in large organs	-Ratio binding/neutralising antibody titres -Histopathology in large organs Induction of cytokines upon vaccination/challenge	For conditional authorisation application

1. Protective efficacy in hamsters

Syrian hamsters were selected as a model system since they can readily be infected with SARS-CoV-2 and have been shown to replicate virus in both the upper and lower respiratory as well as the intestinal tract (Fuk-Woo Chan et al, 2020). The model is not lethal but mimics mild to modest disease severity in humans. The studies will be designed to determine both the protective efficacy and the risk of enhanced disease induction (see below) in a small animal model. This study will consist of two parts that focus on protection from viral replication in the lungs (part 1) and from virus induced pathology (part 2). This will be accomplished by terminating the animals and analysing the data on days where there are maximal viral loads in the lungs and maximal pathology. The timing for maximal viral loads and maximal pathology will be established in pilot studies. Both parts of these studies will assess two different dose levels of CVnCoV to evaluate efficacy following one and two IM injections. This study will be conducted with the non-clinical material manufactured with a process comparable to the clinical material. Animals (5/group) will be assessed for vaccine induced antibody responses after one and two vaccinations. Upon challenge with SARS-CoV-2 four weeks after the second vaccination, animals will be euthanized on d4 (part 1) and d7 (part 2) post challenge. Analyses will include the determination of animal weight, detection of viral titres in the upper and lower respiratory tract, gross pathology and histopathology of target organs (lungs, intestines) as well as cytokine analyses from lung tissue. Data generated in both studies will determine the immune responses elicited in outbred hamsters and the ability of the vaccine to protect small animals from challenge infection.

2. Protective efficacy in NHPs

In order to characterise CVnCoV induced immune responses and protective efficacy in a system that is most likely to be predictive for responses in humans, rhesus macaques were chosen as additional challenge model. Non-human primates including rhesus macaques have been shown to feature high viral replication in both the upper and lower respiratory tract and exhibit overall mild disease with pathogenic features of viral pneumonia. CVnCoV (clinical material) will be analysed for vaccine efficacy and induction of VDE.

NHPs (6/group, male/female) will either receive two doses of buffer as a negative control or CVnCoV at 0.5 or 8 µg. Both cellular and humoral responses upon vaccination will be analysed and challenge with SARS-CoV-2 will take place 4 weeks after the second vaccination. Protection from challenge infection will be assessed by determining levels of virus in the upper and lower respiratory tract. In addition to weight loss and morbidity, pathology induced by viral challenge will be determined via X-ray and CT scanning on different time points post challenge. Comprehensive histopathological analyses will be conducted from all large organs including upper and lower respiratory and intestinal tract, heart, spleen, liver, kidney and brain on the day of termination on day 6 (2 of 6 animals), d7 (2 of 6 animals) and d8 (2 of 6 animals). Additionally, the injection site as well as the draining lymph nodes will be microscopically evaluated.

Data generated in NHP studies will allow conclusions on the immunogenicity, and protective efficacy of CVnCoV.

Background on enhanced disease in SARS-CoV-2

Vaccine-dependent disease enhancement (VDE) has been described in non-clinical models for SARS and MERS-CoV and is associated with vaccine induced Th2-biased responses, the induction of non-neutralising antibodies that can lead to enhanced viral uptake and ultimately to pathological changes in the lung upon infection that exceed changes induced by natural infection. It is believed that the risk of inducing enhanced disease, if present in the context of SARS-CoV-2, can be controlled by developing a vaccine that is able to elicit Th1-biased responses as well as high levels of virus neutralising antibody titres (VNTs) compared to binding antibodies (enzyme-linked immunosorbent assay [ELISA] titres). To date, there is no evidence of VDE in animal models of SARS-CoV-2 including a study testing mRNA vaccines in NHPs (Mercado et al., 2020, Corbett et al., 2020 and van Doremalen et al., 2020) nor clinical evidence that this might be a concern in SARS-CoV infections. CVnCoV leads to a high ratio of functional (VNTs) to binding antibodies (ELISA titres) aimed to induce a Th1 immune response. This is triggered by toll-like receptor 7 stimulation (TLR7) resulting in a Type I IFN induction (see Annex 1), both of which are characteristics that may prevent the development of VDE in the non-clinical models for SARS and MERS-CoV. Based on non-clinical data with CVnCoV (see Annex 1) and CureVac's RNActive® platform, the risk for VDE is considered to only be hypothetical at this time. This is further supported by the presented non-clinical data of CVnCoV showing a balanced immune response with high titres of both IgG1 and IgG2a, high VNTs after 2 vaccinations accompanied by high levels of CD8+ T-cells. The data obtained in mice demonstrate that CVnCoV is a potent vaccine

Pagina's zijn verwijderd 620375

38 - 43

5.1.1c

C. Questions on Clinical Development

Question 12

Does EMA agree with the clinical data package proposed to be submitted in support of the Conditional Marketing Authorisation of CV07050101 for adults 18 and above for the prevention of virologically-confirmed COVID-19 disease?

Question 13

a) Does the EMA agree with the clinical data package proposed to be submitted in support of Marketing Authorisation with regard to?

- *Safety data including preliminary and descriptive VDE assessment*
- *Reactogenicity data*
- *Immunogenicity data*
- *Efficacy data*

b) Does the EMA approve the proposed pooling of studies CV-NCOV-004 and -005 as well as the overall pooling for both safety as efficacy?

c) Does the EMA approve the proposed special populations to provide additional safety, reactogenicity and immunogenicity data, as part of the clinical development plan?

Applicant's Position Questions 12-13

The objective of the development is to achieve an early approval via the conditional marketing authorisation pathway of European Medicines Agency (EMA) in early 2021 followed by standard marketing authorisation during the second half of 2021. In scope for standard marketing authorisation are all age groups and at-risk populations including elderly as well as special populations. Clinical development started in younger healthy adults 18 to 60 years of age (YOA), to assess safety and reactogenicity of different dose levels as well as to perform dose selection. Older adults above 60 YOA, in stable health condition, are being included rapidly in the clinical development to confirm acceptable safety and reactogenicity and to confirm that the selected dose is also accurate for this age group. Based on these data, Phase 2b/3 studies will assess safety and efficacy in larger sample sizes. In parallel, vaccination of people with underlying conditions will commence, as this is the population most at risk for COVID-19.

In all studies, all subjects will be evaluated for safety and a subset for immunogenicity and reactogenicity outcomes. Additionally, in all studies, COVID-19 disease cases and asymptomatic infections will be captured in order to obtain, as rapidly as possible, information on efficacy against COVID-19. A statistical analysis plan for possible pooling of cases will be submitted in the application. In Phase 1 and 2a studies, duration of follow-up for each subject, including for safety, will be minimum 12 months after the last administered dose. In later studies, blinded safety follow-up for all serious adverse events (SAEs), adverse events of special interest (AESIs) including potential immune-mediated diseases (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 studies are performed, whatever occurs first. Thereafter, the control group study participants will be offered the CVnCoV vaccine and safety follow-up until study end will be open and will pertain to vaccine-related SAEs, fatal SAEs as well as pregnancy.

During the full clinical development, an independent data safety monitoring board (DSMB) overviews the programme for safety assessments, and can be involved in assessment of early efficacy or of futility, as appropriate.

The clinical data package proposed to be submitted in support of the **Conditional Marketing Authorisation** takes into consideration the following:

- Safety data in a total of minimum~3500 subjects exposed to a final dose including up to 1000 above age of 60 years irrespective of sero-status at enrolment from studies CV-NCOV-001 (FIH), CV-NCOV-002 (elderly), CV-NCOV-003 (co-morbidities), CV-NCOV-004 (pivotal efficacy) and CV-NCOV-005 (study in Health Care Workers). This includes:

Pagina's zijn verwijderd 620375

45 - 56

5.1.1c

paediatric population is overall not the one most at risk for clinically significant COVID-19 disease, although a medical need exists also in this population. Nevertheless, two studies in an age-de-escalation approach (CV-NCOV-009 and -010) are proposed, to be further discussed with and agreed by with the PDCO as part of the PIP.

While the current clinical development plan is considered comprehensive and sufficient for a stepwise conditional and thereafter unconditional marketing authorisation of CVnCoV, a comprehensive Risk Management Plan (RMP) is proposed to capture potential missing data and further pharmacovigilance surveillance, as detailed in the applicant's position to Questions 17-19. This includes set-up and use of a pregnancy registry.