ANRS 0407s - LKV.Cov40

(Information for researchers)

A phase 1/2 multicenter, randomized study, of the safety and immunogenicity of a sub-unit protein CD40.RBDv bivalent COVID-19 vaccine, adjuvanted or not, as a booster.

Headings	**Content**
In a nutshell	Investigator/Principal Investigator : **Prof. Yves LEVY**
	Structure/teams : Vaccine Research Institute (VRI) ICTA, International CRO Bordeaux vaccine analytics-Adera/Université de Bordeaux LinKinVax
	Study start date/end date (provisional or not) : **29 April 2024/ 6 months after the date of last visit by the last volunteer**
	Number of participants: **240 healthy volunteers**
	Status : ***Under recruitment***
	Pathology: **COVID-19**
	Sponsorship: **Inserm-ANRS MIE**
	Funded as part of : *NA*
The project (250 words max)	A phase 1/2a clinical trial with the primary objective of evaluating the humoral immune response to the new CD40.RBDv vaccine candidate, an anti-CD40 IgG4 monoclonal antibody fused to the RBD (*receptor binding domain*) of the original SARS-CoV-2 Wuhan strain and to an RBDv sequence harbouring mutations common to several coronaviruses. It has been launched by the French *start-up* LinKinVax on the basis of the vaccine platform developed over more than a dozen years by the Vaccine Research Institute (VRI) and supported by the ANRS MIE. Thus, the evaluation of a booster vaccine capable of improving the magnitude and durability of anti-SARS-CoV-2 responses is important. The vaccine studied is a subunit protein vaccine containing both the ancestral SARS-CoV-2 sequence of RBD and the same part of RBD harbouring several mutations shared by several variants, including Omicron.
Latest news (if applicable)	**First inclusion on 27 May 2024.**
Type of study	**Phase 1/2a multicentre, randomised, open-label trial comprising four two-arm, two-part vaccine cohorts**
Main objectives	Primary objective: To assess the tolerance and reactogenicity of vaccine strategies during the first 3 months following each dose. Co-primary objective: To determine the humoral immune response (neutralising antibodies) induced by the vaccine strategies.
Secondary objectives	Secondary objectives: Evaluation and analysis of tolerance and immune response until the end of the trial.

Contents

Main inclusion criteria

1. Age ≥ 18 years and < 85 years
2. Agreement and availability to be monitored and to comply with planned study procedures, visits and calls throughout the study at one of the dedicated investigator centres.
3. Informed, written and signed consent before any selection procedure related to the study is carried out
4. Membership of or benefiting from a social security scheme
5. Agreement to be included in the French Ministry of Health's computerised file (for France only)
6. In good or stable health, according to the clinical judgement of the investigator, as established by medical history, vital signs, clinical examination and biological assessments, with or without a history of previous COVID infection (proven by PCR or antigen test) at least 6 months prior to the screening visit.
7. Having received a primary vaccination and ≥ 1 booster(s) of COVID-19 mRNA vaccine with the last booster at least 6 months before first injection
8. Patients with stable biochemical parameters :
    - ALT, ASAT and alkaline phosphatase < 1.25 × upper limit of normal (ULN)
    - Creatinine :
        - For participants < 65 years of age, creatinine < 1.1 x laboratory ULN
        - For participants ≧ 65 years, Creatinine < 1.4 x laboratory ULN.
9. Haematology parameters :
    - Haemoglobin ≥ 11.0 g/dl for women and ≥ 13.0 g/dl for men
    - Platelets from 125,000 to 550,000/mm3
    - Leukocytes = 3,300 to 12,000 cells/mm3
    - Lymphocytes ≥ 800 cells/mm3
10. Virological tests :
    - Negative serology for hepatitis B surface antigen (HBsAg)
    - Negative serology for hepatitis C virus (anti-HCV) or negative PCR if anti-HCV positive
    - Negative serology for the HIV antigen/antibody screening test or diagnosis of HIV seropositivity, using triple antiviral therapy and with an undetectable viral load (last results less than 1 month old).
11. Normal urinalysis :
    - Absence of urine glucose, and
    - Absence of urine protein or trace protein, and
    - Absence of urinary haemoglobin or trace haemoglobin (if a trace of haemoglobin is

present on the strip, microscopic analysis of urine with a normal level of red blood cells.

12. Volunteers must meet the eligibility criteria for the authorised indication in the RCP of the vaccine (Comirnaty® Original/Omicron BA.4-5).
13. For women of childbearing age: negative serum pregnancy test (βHCG) at the inclusion visit and negative urine pregnancy test on the day of vaccination AND use of an effective method of contraception at least 4 weeks before vaccination and until at least 12 weeks after the last vaccination.

    For male participants, use of an effective method of contraception with their partner from the first day of vaccine administration until at least 12 weeks after the last vaccination administration, this measure also applying to sperm donation.
14. Agreement to perform and receive the results of a screening test for SARS-CoV-2 in accordance with the study protocol.

Main non-inclusion criteria Specific to Research

1. Acute febrile infection (body temperature ≥ 38.0°C) within the previous 72 hours and/or having symptoms suggestive of COVID-19 or SARS-CoV-2 infection within the previous 28 days or having been in contact with an infected person within the 14 days prior to the inclusion visit.
2. Immunosuppressive drugs received during the 3 months preceding the first administration of the vaccine or within 6 months for chemotherapy. (Not excluded: [1] corticosteroid nasal spray; [2] topical corticosteroids for mild uncomplicated dermatitis; or [3] a single course of oral/parenteral corticosteroids at doses < 2 mg/kg/day and duration of treatment < 11 days and terminated at least 30 days prior to inclusion.
3. Immunoglobulins and/or monoclonal antibodies received within 90 days prior to the first administration of the vaccine or administration planned before the end of the study.
4. Blood products, including plasma from convalkescents, received within 120 days prior to the first administration of ME and the planned administration before the end of the study.
5. Any medical condition that could alter the immune response.

   A clinically significant medical condition, abnormal clinical examination findings, clinically significant abnormal laboratory findings or a medical history that has a clinically significant impact on the current state of health. A clinically significant condition or process includes, but is not limited to:

   - a process that affects the immune response;
   - a process that would require treatment to affect the immune response;
   - any contraindication to repeated injections or blood tests;
   - a condition requiring medical intervention or active surveillance to avoid serious danger to the participant's health or well-being during the study period;
   - a condition or process whose signs or symptoms could be confused with reactions to the vaccine;
   - any condition specifically mentioned in the non-inclusion criteria below.
6. DELETED
7. Intention to participate in other research involving an experimental product from 4 weeks prior to the inclusion visit until the end of the study.
8. Pregnancy or breast-feeding in progress, or positive pregnancy test at the inclusion visit.
9. History of serious adverse events following vaccine administration, including anaphylactic reaction and associated symptoms, rash, breathing difficulties, angioedema and/or abdominal pain,

or a history of an allergic reaction that may be triggered by a component of the SARS-CoV-2 vaccine at the time of the first vaccine injection (a volunteer who experienced a non-anaphylactic adverse reaction to pertussis vaccine in childhood will not be excluded).

10. Any bleeding disorder considered to be a contraindication to intramuscular injection, previous phlebotomy or the administration of anticoagulants.
11. Subjects under legal protection (guardianship, curatorship, etc.)
12. A condition that requires active medical intervention or monitoring to avoid a serious threat to asthma other than mild, well-controlled asthma (symptoms of asthma severity, as defined in the latest report by the National Asthma Education and Prevention Program (NAEPP) expert panel).

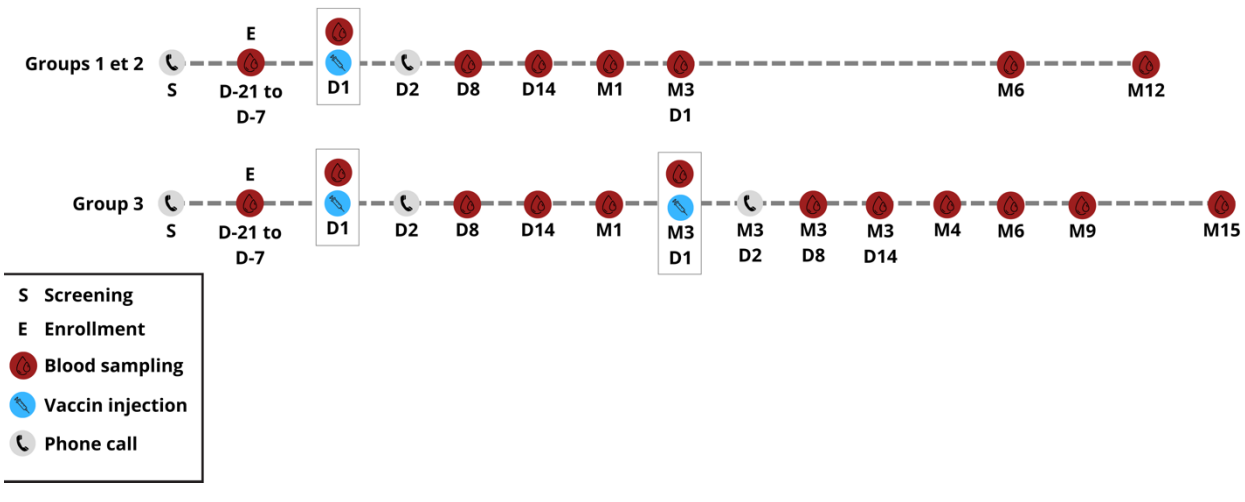
    Exclusion of a volunteer who :

    - Use a short-acting rescue inhaler (usually a beta-2 agonist) every day; or
    - Uses moderate/high dose inhaled corticosteroids; or
    - In the past year has had one of the following criteria: (i) more than one exacerbation of symptoms treated with oral/parenteral corticosteroids or (ii) required emergency care, hospitalisation or intubation for asthma.

13. Hypertension :

    - If a diagnosis of hypertension has been made, poorly controlled blood pressure (controlled blood pressure is defined as ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic, with or without medication, with only isolated and brief cases of higher figures, which must remain ≤ 150 mmHg systolic and ≤ 100 mmHg diastolic) must be excluded. For these volunteers, blood pressure must be ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic at inclusion.
    - If a diagnosis of hypertension has NOT been made for an individual, a systolic blood pressure ≥ 150 mm Hg at inclusion or a diastolic blood pressure ≥ 100 mm Hg at inclusion (measurement should be taken on a recumbent individual for at least 5 minutes and repeated at the end of the consultation, if appropriate) should be excluded. Blood pressure should be confirmed outside the clinical centre to rule out hypertension.

14. BMI ≥ 40 kg/m2; ≤ 18 kg/m2; or BMI ≥ 35 kg/m2 with at least 2 of the following parameters: age > 45 years, current smoker, known hyperlipidaemia, blood pressure defined as consistently ≥ 140 mm Hg systolic and ≥ 90 mm Hg diastolic.
15. Malignant tumour (not excluded: volunteer with a surgically excised malignant tumour who, in the opinion of the investigator, has a definite probability of durable cure or is unlikely to develop a recurrence of the malignant tumour during the study period).
16. Asplenia: any condition resulting in the absence of a functional spleen.
17. History of seizure disorders in the last 3 years. Volunteers who have received medication to prevent or treat seizure(s) at any time in the last 3 years will be excluded.
18. History of hereditary angioedema, acquired angioedema or idiopathic angioedema.
19. History of myocarditis, pericarditis, cardiomyopathy, congestive heart failure with permanent sequelae, clinically significant arrhythmia (including arrhythmia requiring medication, treatment or clinical follow-up).
20. History of autoimmune disease
21. Any medical, professional or other condition which, in the opinion of the investigator, would interfere with compliance with the protocol, the evaluation of safety or reactogenicity, or the ability of a volunteer to give informed consent or would constitute a contraindication to these activities.

	22. Psychiatric conditions preventing compliance with the protocol. In particular, volunteers with a history of psychosis in the last 3 years, a current risk of suicide or a history of attempted suicide or suicidal gesture are specifically excluded. 23. Live attenuated vaccines (e.g. measles, mumps and rubella [MMR]; varicella; yellow fever) received within 30 days prior to the first administration of the experimental vaccine or scheduled within 28 days of the last injection in accordance with the protocol. 24. Vaccines that are not live attenuated vaccines and that have been administered in the 21 days preceding the first administration of the experimental vaccine (e.g. tetanus, pneumococcus, hepatitis A or B). 25. Anti-allergy treatment with antigen injections for 30 days prior to the first administration of the experimental vaccine and until the end of the study.
Primary endpoint:	Primary safety endpoint: proportion of participants with no solicited grade 3 or 4 local/systemic biological or clinical AEs, or unsolicited AEs between Day 1 and Month 3 after each administration of the investigational medicinal product (IMP)/vaccine and considered possibly related to the administration of the IMP. Primary immunogenicity endpoint: Neutralising antibody titres (anti-RBD) to D614G and circulating VOCs at baseline, up to 1 month (M1) after each dose: geometric mean of antibody titres and seroconversion rate (at least 4-fold increase in antibody titres between baseline and month 1).
Secondary endpoint(s) :	Secondary safety endpoints: Tolerance and reactogenicity to the end of the trial: number of volunteers with solicited local and systemic Adverse Reactions (ARs) [schedule: up to Day 8]; number of volunteers with Adverse Events (AEs) other than solicited adverse events [schedule: Day 1 to Month 3 after each dose]; number of volunteers with serious AEs (SAEs), grade 3 or grade 4 [schedule: Day 1 to Month 3 after each dose]; number of volunteers with events leading to discontinuation of the vaccination schedule. Secondary immunogenicity endpoints : - Humoral immune response (binding antibody titres): geometric mean of antibody titres and seroconversion rate. - Cross-neutralisation against relevant VOCs (neutralising antibody titres): for each VOC, geometric mean of antibody titres and increase between baseline and month 1. - Correlation between the magnitude of specific CD4+ T cell responses and specific IgG response rates at each protocol endpoint: spearman correlation coefficient. ANRS 0407s- LKV.Cov40 -- French version Version 3.0 based on protocol V4.0 04/06/2024 Page 2 of 2 - Vaccine efficacy against COVID-19: number of COVID-19 infections (PCR or antigen test +) and severity (as defined by the CDC) in participants throughout the study. - Expression of CD4+ and CD8+ T cell cytokines measured by ICS at each protocol-defined endpoint: magnitude (percentage of cells producing at least one cytokine).
Monitoring procedures ***(Protocol V4)***	

Data and samples collected	**Biotech libraries**	**-serum** **-plasma** **-saliva**
	Data	**-**

B - How to access the collection

1- project submission: **via the sample request form on the website**

2- project assessment: **scientific committee or independent experts**

3- Making the collection available**: final decision by ANRS MIE management or Scientific Council**

Contact e-mail address for submitting your project: **biobanque@anrs.fr**

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