**ANRS VRI06** - Information for researchers

**Title** : A phase I multicenter double-blind placebo controlled dose escalation trial of an adjuvanted anti-CD40 mAb fused to Env GP140 HIV clade C ZM-96 (CD40.HIVRI.Env) vaccine combined or not with a DNA-IV-PT123 HIV-1 vaccine in healthy participants

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| In brief | Investigator: Pr Yves Lévy |
| | Structure/teams:<br>ANRS MIE - Clinical Research & Pharmacovigilance Departments (Paris)<br>Vaccine Research Institut (VRI, Créteil)<br>UMS 54 MART (Bordeaux)<br>Inserm U1219/Inria SISTM (Bordeaux)<br>Inserm U955 - Equipe 16 - Immunomonitoring Platform (Créteil)<br>Inserm U1109 - Institute of Virology (Strasbourg)<br>CHUV- Division of Immunology and Allergy (Lausanne) |
| | Start dates : 31/03/2021<br>End date of research: 29/11/2024 |
| | Number of participants: 72/72 |
| | Research status: Completed |
| | Pathology: HIV |
| | Promotion: Inserm - ANRS MIE |
| | Funded under: VRI/ANRS MIE vaccination program |
| The project | The vaccine candidate "CD40.HIVRI.Env" is a monoclonal antibody that specifically targets CD40 receptors located on the surface of dendritic cells. The antibodies are coupled with HIV envelope antigens in order to deliver the antigen directly to dendritic cells and generate a strong immune response.<br>The ANRS VRI06 trial aims to evaluate this vaccine candidate in 72 healthy volunteers. It is a phase I, multicenter, double-blind, placebo-controlled, dose-escalation trial conducted in France and Switzerland to evaluate different doses (0.3, 1, and 3 mg) of the CD40.HIVRI. Env adjuvanted with Hiltonol®, administered alone (Solo groups) or co-administered with the DNA-HIV-PT123 vaccine (Combi groups) at weeks W0, W4, and 24. Participants will be randomized into one of the six trial groups to receive the active vaccine strategy or placebo in a 5:1 ratio. Enrollment in a given group (other than the "Solo 0.3" group) will be opened based on criteria derived from safety data from the previous group(s).<br>An additional booster dose (part 2 of the trial) will be administered late (Late Boost of CD40.HIVRI.Env post W48) and follow-up will be conducted 2 weeks ($W_{LB+02}$) and 24 weeks ($W_{LB+24}$) after the "Boost" ($W_{LB}$). Volunteers (n=60) who received the active vaccination in part 1 of the trial will be randomized in a single-blind manner to receive a 0.3 mg dose of the CD40.HIVRI.Env vaccine, either with or without adjuvant. |
| Latest news | CROI 2025 of 9 and 12 March at San Francisco Abstract accepted as a poste « Un-Adjuvanted CD40.HIVRI.ENV Vaccine Late Boost Induces Durable Immune Responses : ANRS/VRI06 Trial » |
| Publication references | https://doi.org/10.1016/j.eclinm.2024.102845 |

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| Type of study | RIPH1 vaccine trial, prospective, multicenter, randomized versus placebo |
| Main objectives | To assess the safety of three dose levels of CD40.HIVRI.Env (0.3; 1; 3 mg) adjuvanted with poly-ICLC (Hiltonol®), alone and in combination with DNA-HIV-PT123, administered at W0, W4 and W24 in healthy volunteers (part 1 of trial). |
| Secondary objectives | Part 1:<br>To assess the capacity of poly-ICLC-adjuvanted CD40.HIVRI.Env alone and in combination with DNA-HIV-PT123 to elicit immune responses against HIV (immunogenicity):<br>• Humoral (antibody) responses;<br>• B-cell responses;<br>• T-cell responses.<br>Part 2:<br>Evaluate the tolerance of administering a booster dose (0.3 mg of CD40.HIVRI.Env alone or with adjuvant) between $W_{LB+02}$ and $W_{LB+24}$ (2 and 24 weeks after the booster dose (Late Boost)).<br>Evaluate the evolution of long-term vaccine responses (immunogenicity) and the effect of a booster dose of CD40.HIVRI.Env. The tests used to monitor the evolution of immune responses will be identical to those performed in part 1 of the trial. |
| Link to research website | https://clinicaltrials.gov/study/NCT04842682 |
| **Inclusion criteria** | Main criteria:<br>• Age of 18 to 65 years<br>• Assessed by the clinic staff as being at "low risk" for HIV infection<br>• Normal biological values<br>  ○ Hemoglobin ≥ 11.0 g/dL for participants who were born female, ≥ 13.0 g/dL for participants who were born male<br>  ○ White blood cell count = 3,300 to 12,000 cells/$mm^3$<br>  ○ Total lymphocyte count ≥ 800 cells/$mm^3$<br>  ○ Platelets = 125,000 to 550,000/$mm^3$<br>  ○ ALT, AST, and alkaline phosphatase < 1.25 xN; creatinine <1.1x N<br>  ○ Negative HIV-1 and -2 blood test<br>  ○ Negative Hepatitis B surface antigen (HBsAg)<br>  ○ Negative anti-Hepatitis C virus antibodies (anti-HCV), or negative HCV polymerase chain reaction (PCR) if the anti-HCV is positive.<br>  ○ Normal urine test: absence of glucose, protein and hemoglobin |
| **Non-inclusion criteria** | Main criteria:<br>• Intent to participate<br>• Clinically significant medical condition, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:<br>  ○ A process that would affect the immune response<br>  ○ A process that would require medication that affects the immune response<br>  ○ A condition or process for which signs or symptoms could be confused with reactions to vaccine |

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| | • Immunodeficiency<br>• Asthma other than mild, well-controlled asthma<br>• Diabetes type 1 or type 2, including cases controlled with diet alone<br>• Thyroidectomy, or thyroid disease requiring medication during the last 12 months<br>• Hypertension:<br>• Contraindication to the IMPs including hypersensitivity<br>• BMI ≥ 40 kg/$m^2$ ; ≤ 18 kg/$m^2$ ; or BMI ≥ 35 kg/$m^2$ with 2 or more of the following: age > 45, systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, current smoker, known hyperlipidemia<br>• Bleeding disorder diagnosed by a doctor (e.g., coagulation factor deficiency, coagulopathy, or platelet disorder requiring special precautions)<br>• Malignancy (Not excluded: participant who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure, or who is unlikely to experience recurrence of malignancy during the period of the study)<br>• Asplenia: any condition resulting in the absence of a functional spleen<br>• Seizure disorder: History of seizure(s) within past three years. Also exclude if participant has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.<br>• History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.<br>• History of myocarditis, pericarditis, cardiomyopathy, congestive heart failure with permanent sequelae, clinically significant arrhythmia (including arrhythmia requiring medication, treatment, or clinical follow-up<br>• History of autoimmune disease<br>• Serious adverse reactions to vaccines including anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain<br>• HIV vaccine(s) received in a prior HIV vaccine trial<br>• Non-HIV experimental vaccine(s) received within the last 5 years in a prior vaccine trial.<br>• Live attenuated vaccines (e.g., measles, mumps, and rubella [MMR]; varicella; yellow fever) received within 30 days before first IMP administration or scheduled within 28 days after one of the 3 injections according to the protocol<br>• Vaccines that are not live attenuated vaccines and were received within 21 days prior to first IMP administration<br>• COVID-19 vaccine received or scheduled within the last 4 weeks before and after one of the 3 injections<br>• Blood products received within 120 days before first IMP administration<br>• Immunoglobulin received within 60 days before first IMP administration<br>• Current anti-tuberculosis (TB) prophylaxis or therapy<br>• Allergy treatment with antigen injections within 30 days before first IMP administration or that are scheduled within 14 days after first IMP administration<br>• Immunosuppressive medications received within last three months before first IMP administration. (Not excluded: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatitis; or |

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| | [4] a single course of oral/parenteral corticosteroids at doses < 2 mg/kg/day and length of therapy < 11 days with completion at least 30 days prior to enrolment) |
| **Primary endpoints** | Proportion of participants without any grade 3 or 4 biological or clinical solicited local/systemic or unsolicited AEs between W0 and W48 (6 months after the last IMP administration), considered to be related or possibly related to IMP administration. |
| **Secondary endpoints** | Part 1:<br>• Safety outcomes between W0 and W48:<br>Safety outcomes will be assessed in real time during the entire follow-up of each participant. In addition, safety analysis will be done two weeks after each injection (W2, W6, W26):<br>○ Unsolicited adverse events: overall ; by grade ; by relationship to the vaccine<br>○ Solicited local and systemic adverse events: overall ; by grade<br>○ Serious adverse events: overall ; by grade; by relationship to the vaccine<br>○ Events leading to discontinuation of the vaccine regime<br>• Immunogenicity endpoints between W0 and W76:<br>Immunogenicity endpoints will be evaluated 2 weeks after each injection of vaccine(s) (i.e. W2, W6, W26 and W48 and W76 for durability):<br>○ Response rate, magnitude, breadth and durability of IgG against Env<br>○ Response rate, magnitude, breadth of neutralizing antibody responses against tier 1 and tier 2 HIV-1 isolates<br>○ Antibody functionality, ADCC at the peak of HIV specific Ab response<br>○ Reponse rate and magnitude of B cell responses<br>○ Response rate, magnitude, polyfunctionality of the CD4 and CD8 T-cells responses<br>• Immunogenicity assays:<br>○ HIV-specific Env binding (BAMA) against various envs and V1/V2 proteins<br>○ Ab functionality (neutralizing Ab responses with the TZM-bL neutralization assay and ADCC function)<br>○ B cell Elispot responses<br>○ CD4 and CD8 T cells responses to Env and other viral antigens measured by ICS (IFN-γ, TNF-α and IL-2)<br>○ Cell subpopulation phenotyping by flow cytometry<br>• Exploratory immunogenicity endpoints between W0 and W76<br>○ Changes in gene expression profile in the whole blood assessed by RNA Seq<br>○ Measurement of cytokine secretion after specific stimulation of cells by Luminex technology<br>○ Association between HLA genotype and immune responses to the vaccine<br>○ Blood cells extended phenotyping by mass cytometry (CyTOF)<br>Part 2:<br>• Tolerance between $W_{LB}$ and $W_{LB+24}$:<br>Tolerance will be assessed in real time during long-term follow-up of each participant in the same manner as for the first 3 points in Part 1. |

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## A - Study methodology and type of data and/or samples collected

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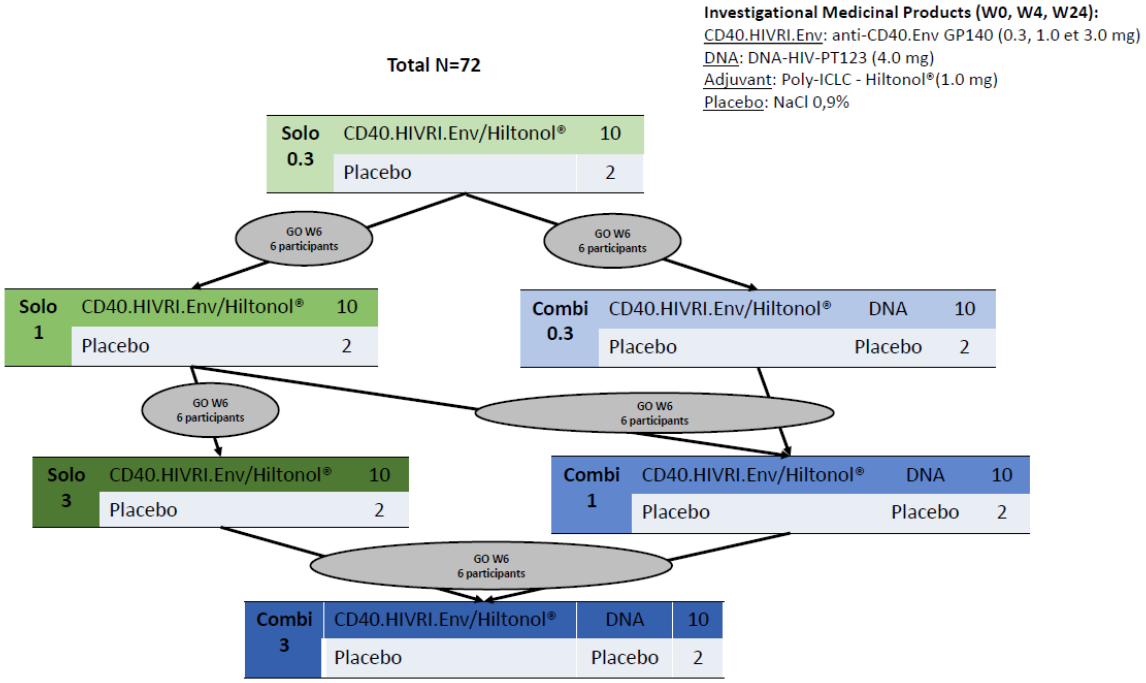
| **Data and samples collected** | **Biotech libraries** | • Whole blood (EDTA and Tempus® tubes)<br>• Serum<br>• PBMC<br>• Plasma (except at W76) |
| | **Data** | • Immunological<br>• Tolerance<br>• Clinical |

**Trial design:** dose-escalation (part 1)

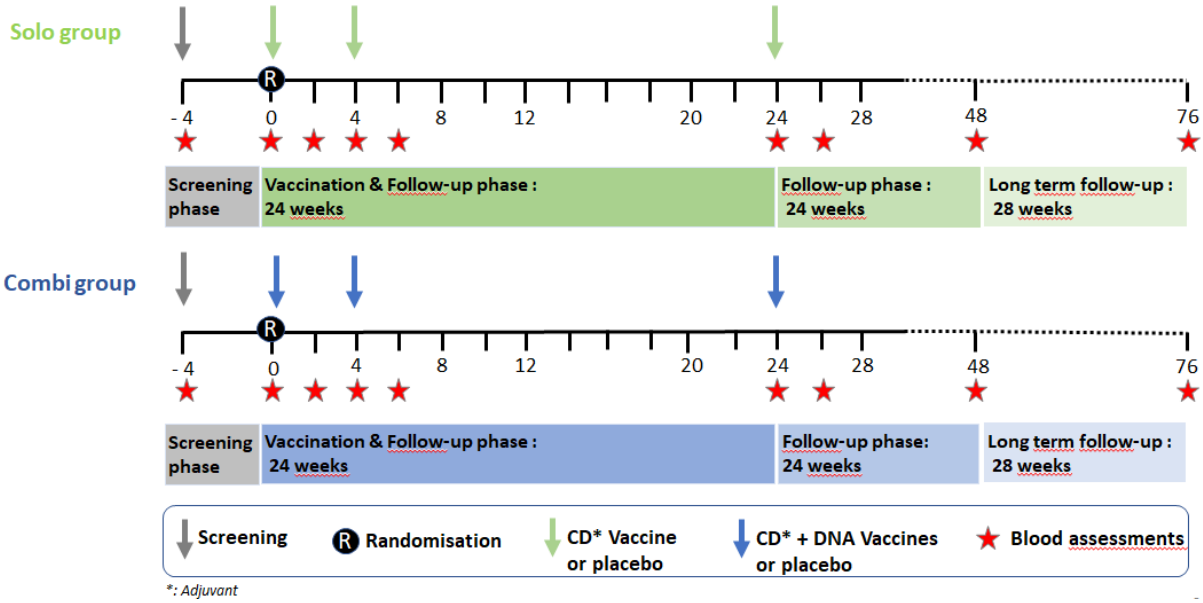



**Sampling schedule:**

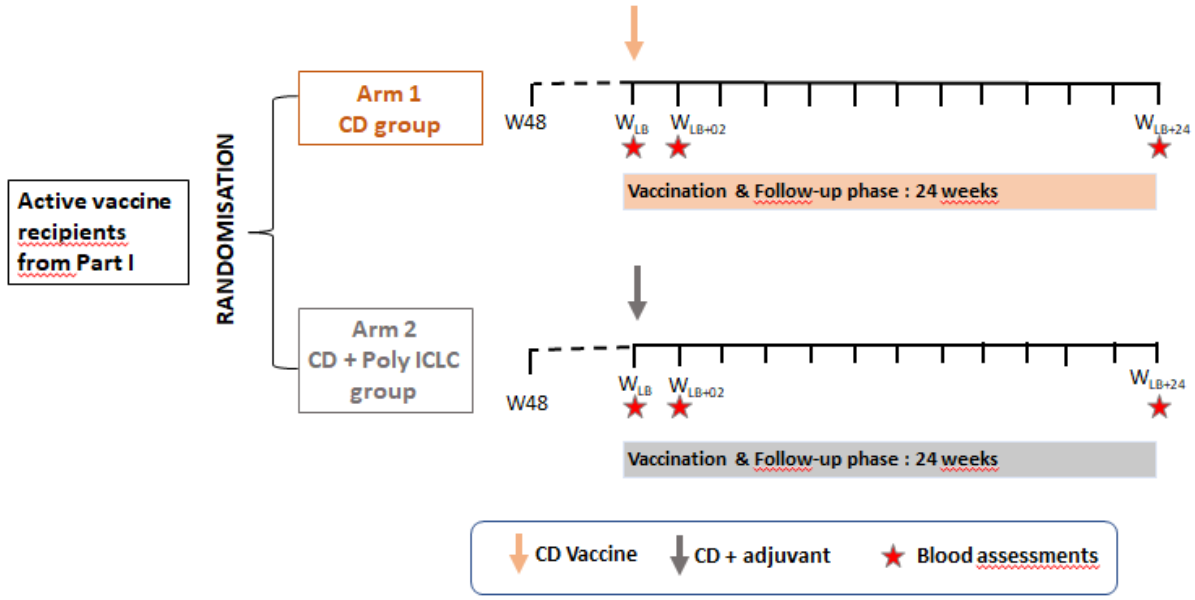
Part 1: at W0, W2, W4, W6, W24, W26, W48 and ± W76
Part 2: à $W_{LB}$, $W_{LB+02}$ and $W_{LB+24}$

**Follow-up modalities:**

**Part 1:**




**Part 2:**




## B - How to access the collection

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

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

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

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