Clinical trial results:
A Phase II randomised, placebo-controlled trial of vedolizumab with or without therapeutic HIV MVA vaccine in individuals who started antiretrovirals during primary or chronic infection

Summary

EudraCT number	2019-002818-40
Trial protocol	FR GB ES DE IT
Global end of trial date	12 July 2023

Results information

Result version number	v1 (current)
This version publication date	28 July 2024
First version publication date	28 July 2024

Trial information

Trial identification

Sponsor protocol code	EHVA_T02/ANRS_VRI07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04120415
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inserm-ANRS MIE
Sponsor organisation address	2, rue d'Oradour-sur-Glane, Paris, France, 75015
Public contact	EHVA, MRC CTU at UCL, +44 (0)2076704783, MRCCTU.EHVA@ucl.ac.uk
Scientific contact	EHVA, MRC CTU at UCL, +44 (0)2076704783, MRCCTU.EHVA@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2023
Global end of trial reached?	Yes
Global end of trial date	12 July 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

EHVA_T02 is a phase II randomised, placebo-controlled trial of vedolizumab with or without therapeutic HIV MVA vaccine in people living with HIV. The main objective of the study will be to assess the impact of vedolizumab and vaccination with MVA upon viral control following analytic treatment interruption (ATI).
Enrolment in the trial commenced in late June 2022. However, it proved to be very challenging to recruit sufficient numbers of participants, which meant that the study most likely could not be completed as planned. This triggered a decision by the trial team and EHVA, in consultation with the trial authorities and representatives of the European AIDS Treatment Group, to stop enrolment in the trial, and the administration of the study products, in order to safeguard the interests of participants already included in the trial. Only two participants have been enrolled and were followed up as per protocol without analytic treatment interruption.

Protection of trial subjects:

An Independent Data Monitoring Committee (IDMC) was formed to assure that the interest of the participants was well served. Among its tasks, the IDMC could recommend trial modification, treatment discontinuation or premature closure.

Background therapy:

Participants were scheduled to continue on their combination antiretroviral therapy (cART) through to week 18 when they were scheduled to interrupt treatment provided it was safe to do so.
All participants were scheduled to resume therapy after the 24 weeks of interruption.
They may have resumed cART earlier under any of the following circumstances:
* 100,000 copies/ml or more of HIV RNA virus, confirmed
* CD4 falls to 350 cells/mm^3 or less, confirmed
* symptomatic HIV progression or an AIDS defining illness
* pregnancy in a female participant
* COVID-19 confirmed
As participation in the trial is entirely voluntary, they had the possibility to resume their cART at any time during the protocol treatment interruption, or not to resume therapy after 24 weeks, without penalty or loss of benefits to which they are otherwise entitled.

Evidence for comparator:

MVA HIV-B (MVATG17401) Vaccine Candidate
MVA HIV-B was only administered to healthy volunteers in a single clinical trial (ANRS VR101 NCT02038842). The trial was an open label study to assess safety and immunogenicity of 4 prime-boost combinations of HIV vaccine candidates (MVA HIV-B/LIPO-5; LIPO-5/MVA HIV-B; GTU-MultiHIV B/LIPO-5; GTU-MultiHIV B/MVA HIV-B). Primary objectives were to assess safety of MVA HIV-B and discard vaccination strategies with an insufficient level of immunogenicity.
Vedolizumab
Two clinical trials have evaluated Vedolizumab alone to determine whether HIV replication can be controlled in the absence of ART. The first study conducted at NIH (NCT02788175) enrolled 26 chronically HIV-1 infected patients on ART. The second study (NCT03147859) evaluating the effects of two doses of Vedolizumab intervention on virus control after ATI has been conducted in Canada in a limited number (n=8) of chronically infected individuals.
The Study Hypothesis
The synergistic actions of MVA and vedolizumab support the scientific rationale for combining these products. These include: a) the induction and potentiation of the HIV-specific CD8 T-cell response by MVA and b) the reduction of trafficking of CD4 T cells in a privileged anatomic compartment such as the gut thus reducing the pool of target cells for HIV infection.

Actual start date of recruitment	14 April 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	2
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The total sample size was calculated as 69 participants (23 per group).

Pre-assignment

Screening details:

INCLUSION CRITERIA
HIV1
18–65
Nadir CD4 count >350 cells/mm3
CD4 count at screening >500 cells/mm3
Viral load less than 50 copies/ml at screening
Started cART after 2009 and on cART for at least one year prior to screening
EXCLUSION CRITERIA
HIV2
VL >200 copies/ml on 2 occasions in 12 months prior to screening
Previous virological failure

Pre-assignment period milestones

Number of subjects started	3[1]
Number of subjects completed	2

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Non-randomisation: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Three subjects were screened, but two randomised

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)

Arm description:

Participants were scheduled to receive vaccine (MVA HIV-B) at week 0 and week 8; and mAb infusion (vedolizumab) at weeks 10, 12, 16, 20, 24, 28, and 32.

Arm type	Experimental
Investigational medicinal product name	Vaccine (MVA HIV-B)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Solution for injection

Dosage and administration details:

The vaccine is a solution of HIV MVA vectors in S08 buffer (10mM Tris/hydrochloride (Tris/HCl), Saccharose 5% (w/v), 10mM Sodium Glutamate (Na Glu), 50mM Sodium Chloride (NaCl), water PPI, pH 8.0).
The vaccines are provided in sealed glass vials and contain a recoverable volume of 0.5ml.
0.5ml of MVA HIV-B (1 x 108 pfu/ml) will be administered intramuscularly in the deltoid muscle of the non-dominant upper arm.

Investigational medicinal product name	mAb infusion (vedolizumab)
Investigational medicinal product code	
Other name	ENTYVIO
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The mAb is provided as 300mg of lyophilized vedolizumab in a single use 20 ml glass vial.
Vedolizumab must be reconstituted with 4.8 ml of sterile water for injection, using a syringe with a 21-25 gauge needle, avoiding excessive foaming, inversion or vigorous shaking. Once completely reconstituted; 5 ml should be withdrawn using a syringe with a 21-25 gauge needle and added to 250 ml of sterile 0.9% sodium chloride solution in an infusion bag.
After reconstitution it should be kept at room temperature (20°C-25°C). It does not contain preservatives and once reconstituted, it should be used as soon as possible. However, it may be stored for up to four hours at 2°C-8°C.
Vedolizumab is administered as an intravenous infusion over 30 mins in the dominant arm. It must not be administered as an intravenous push or bolus. After infusion, the line should be flushed with 30ml of normal saline. The mAb must be administered by healthcare professionals prepared to manage hypersensitivity.

Arm title	Placebo vaccine + placebo infusion

Arm description:

Participants were scheduled to receive placebo vaccine at week 0 and week 8; and placebo infusion at weeks 10, 12, 16, 20, 24, 28, and 32.

Arm type	Placebo
Investigational medicinal product name	Placebo vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Solution for injection

Dosage and administration details:

The placebo for MVA HIV-B used in this trial is a solution composed of S08 buffer (as for the MVA vaccine).
Vials are the same as for the MVA vaccine.
0.5ml of placebo for MVA (S8 buffer) will be administered intramuscularly in the deltoid muscle of the non-dominant upper arm.

Investigational medicinal product name	Placebo infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sodium Chloride (NaCl) for infusion, 0.9% in 250 ml infusion bags.
The placebo infusion should also be administered as an intravenous infusion over 30 minutes as per vedolizumab.

Number of subjects in period 1	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)	Placebo vaccine + placebo infusion
Started	1	1
Completed	0	0
Not completed	1	1
Early termination of the trial	1	1

Baseline characteristics

End points

End points reporting groups

Reporting group title	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)
Reporting group description:	
Participants were scheduled to receive vaccine (MVA HIV-B) at week 0 and week 8; and mAb infusion (vedolizumab) at weeks 10, 12, 16, 20, 24, 28, and 32.	
Reporting group title	Placebo vaccine + placebo infusion
Reporting group description:	
Participants were scheduled to receive placebo vaccine at week 0 and week 8; and placebo infusion at weeks 10, 12, 16, 20, 24, 28, and 32.	

Primary: Area under the HIV RNA curve from treatment interruption (scheduled for 18 weeks after entering the trial) to 24 weeks post-treatment interruption

End point title	Area under the HIV RNA curve from treatment interruption (scheduled for 18 weeks after entering the trial) to 24 weeks post-treatment interruption[1]
End point description:	
End point type	Primary
End point timeframe:	
From treatment interruption (scheduled for 18 weeks after entering the trial) to 24 weeks post-treatment interruption	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Early termination of the trial

End point values	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)	Placebo vaccine + placebo infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: log10 copy-weeks/ml				
arithmetic mean (confidence interval 97.5%)	(to)	(to)		

Notes:

[2] - Early termination of the trial

[3] - Early termination of the trial

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of randomisation until 30 days after the last protocol visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)

Reporting group description:

Participants were scheduled to receive vaccine (MVA HIV-B) at week 0 and week 8; and mAb infusion (vedolizumab) at weeks 10, 12, 16, 20, 24, 28, and 32.

Reporting group title	Placebo vaccine + placebo infusion

Reporting group description:

Participants were scheduled to receive placebo vaccine at week 0 and week 8; and placebo infusion at weeks 10, 12, 16, 20, 24, 28, and 32.

Serious adverse events	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)	Placebo vaccine + placebo infusion	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Vaccine (MVA HIV-B) + mAb infusion (vedolizumab)	Placebo vaccine + placebo infusion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
Injury, poisoning and procedural complications			
Tooth injury			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2019	• Post menopausal expanded (summary and section 3.1 inclusion criteria) • Vital signs specified – temperature, blood pressure, pulse and respiratory rate (table 1 schedule, sections 6.3.1 & 6.3.3) • TB screening added to schedule and section 6.2 • Unblinding clarified to reflect investigators responsibilities (section 5.4)
07 November 2019	• Nadir CD4 upped from 300 to 350 (summary and section 3.1 inclusion criteria) • Kaposi's sarcoma changed from included to excluded (summary & section 3.2 exclusion criteria) • Section 6.8 anonymised replaced by pseudonymised (indirectly identifiable) • Section 7.4 sponsor responsibilities in regard to safety reporting amended to reflect local requirements • Section 10.1 and schedule amended to reflect extra blood tests required pre-leukapharesis • Section 11.5 added to reflect reporting requirements at the end of the trial • Section 9 Statistical methods updated • The second pre-specified safety analysis is when the 15th participant enrolled has their safety visit two weeks following administration of vedolizumab/placebo (week 12) • Clinicaltrial.gov number added to cover and in text • Patient replaced by participant throughout for consistency • Chloride added to table 5 to be consistent with Sodium • Minor formatting changes

03 September 2021	Cover – logos updated and ANRS director change Pages ii to v - Trial Administration – update to staff Page vi to xii - update to summary based on other protocol changes Table 1 – updated to clarify timings Introduction – section 1.4.2 updated for later studies at request of IDMC (references added in section 19), 1.7 at request of German regulator Section 3.1 – inclusion criteria updated to take account of COVD-19 vaccinations Section 4.2 – clarification made as per LOA #1 (previously approved as amendment in UK, Switzerland and France) Section 5.4 – unblinding clarification made as per LOA #1 (previously approved as amendment in UK, Switzerland and France) Section 5.5– COVID-19 confirmed added to treatment discontinuation and schedule clarification to allow for discontinuation Section 5.9.5 – updated to take account of COVID-19 vaccinations and boosters Section 6.1.2 – added to cover SARS-CoV2 testing Section 6.3 - clarification made as per LOA #1 (previously approved as amendment in UK, Switzerland and France), extra questionnaire added to cover COVID-19 Section 6.3.4 – clinic timing clarified Section 6.3.5 – name of checklist changed to clarify Section 6.3.7 – updated to clarify Section 6.3.8 – questionnaire deleted and placed in correct section (6.4) Section 6.4, section 6.6, section 6.8 - schedule clarification to allow for discontinuation of or not starting ATI Section 7.1.3 – updated so that hospitalisations are not excluded Section 7.2.1 – COVID-19 added as a notable event as leads to discontinuation Section 7.4 - updated Sponsor role Section 8.1.1 –COVID-19 added to cover COVID-19 in relation to starting/stopping ATI Section 8.1.4 – volume of blood added at request of German regulator Section 8.3 – remote monitoring added to cover monitoring if visits to sites are not possible due to pandemic Section 9 – additions made at request of German regulator General – minor format changes and spelling corrections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported