Clinical trial results:
EHVA T01(European HIV Vaccine Alliance Therapeutic Trial 01)/ANRS VRI05: A Phase I/II randomised therapeutic HIV vaccine trial in individuals who started antiretrovirals during primary or chronic infection

Summary

EudraCT number	2017-003081-27
Trial protocol	GB FR ES IT
Global end of trial date	11 July 2019

Results information

Result version number	v1 (current)
This version publication date	12 June 2020
First version publication date	12 June 2020

Trial information

Trial identification

Sponsor protocol code	EHVAT01/ANRSVRI05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02972450
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inserm-ANRS
Sponsor organisation address	101 Rue de Tolbiac, Paris, France, 75013
Public contact	EHVA, MRC CTU at UCL, 44 02076704783, mrcctu.ehvat01tmt@ucl.ac.uk
Scientific contact	EHVA, MRC CTU at UCL, 44 02076704783, mrcctu.ehvat01tmt@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	20 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2019
Global end of trial reached?	Yes
Global end of trial date	11 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

We are testing therapeutic HIV vaccines with or without an antibody in people who are HIV positive on treatment. Therapeutic means it might benefit people who are HIV positive.
We want to find out if the products help the immune system control the virus.
We are testing a combination of two vaccines. They are GTU-MultiHIV B-clade DNA and MVA HIV-B. One aims to generate a response from your immune system and the second to boost these responses (a prime-boost regimen).
We are also testing a monoclonal antibody called vedolizumab which is given by infusion. Monoclonal means it is made by identical cells, all clones of a cell of the immune system. Vedolizumab might reinforce the action of the immune system against HIV. It might reduce spread of HIV replication and make the immune system control the HIV infection even when antiretroviral treatment is stopped.
The four randomisation arms will be:
*Vaccines
*Monoclonal antibody (mAb) vedolizumab
*Vaccines with mAb vedolizumab
*Placebo

Protection of trial subjects:

An Independent Data Monitoring Committee (IDMC) was formed. The IDMC could recommend premature closure or reporting of the trial, or that recruitment to any research arm be discontinued.

Background therapy:

Participants were scheduled to continue on their combination antiretroviral therapy (cART) through to week 24 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 the following circumstances:

* Disease Progression
* CD4 falls to 350 or less cells/mm^3 (confirmed)
* Viral load rises to 10,000 copies/ml or more confirmed
* Pregnancy

As the participant’s participation in the trial is entirely voluntary, they may choose 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. Although the participant is not required to give a reason for doing so, a reasonable effort should be made to establish this reason while fully respecting the participant's rights.

Evidence for comparator:

GTU-MultiHIV B DNA Vaccine
The GTU-MultiHIV B clade vaccine has been tested extensively in preclinical and phase I/II clinical studies.

MVA HIV-B Vaccine
MVA HIV-B has only been given to healthy volunteers in one study (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.

Rationale for Combining the GTU-MultiHIV B DNA and MVA HIV-B Vaccines
Priming with DNA has been shown to augment breadth and magnitude of T-cell and B-cell responses upon boosting with attenuated pox viruses including MVA. A strong rationale for combining GTU-MultiHIV and MVA HIV-B vaccines in a prime boost strategy in this population is that these two vaccines share homologous HIV sequences and CTL epitopes.

Vedolizumab
NIH have conducted a trial in 20 HIV-1 positive participants to see if vedolizumab is safe and can control the VL when treatment was interrupted.

Rationale for Combining the MVA HIV-B and GTU-MultiHIV B DNA Vaccines and Vedolizumab
Assuming that the effect and therefore the mechanism of action of vedolizumab will be similar to that seen recently in macaques, the hypothesis is vedolizumab will limit spread of virus through an effect on CD4+ T-cell movement in the gut, and this will synergise with the DNA/MVA vaccines to further augment the anti-viral T-cell response, and enhance the ability to eliminate viral reservoir and preserve CD4+ T-cells in GI tract. Preservation of CD4+ T-cells in HIV patients has been shown to improve prognosis. If this is combined with elimination/reduction of HIV reservoir either by vedolizumab alone or combined with DNA/MVA there might be a measureable delay in viral rebound and increase in CD4+ T-cells.

Actual start date of recruitment	20 February 2019
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	Switzerland: 1
Worldwide total number of subjects	1
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)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The total number of patients randomised to each arm and the duration of the trial will depend on the number of arms passing through the interim stage. The total sample size was calculated as between 88-192 patients. Main eligibility criteria below.

Pre-assignment

Screening details:

INCLUSION CRITERIA
HIV1
18–65
Nadir CD4 count >300 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	1

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Non-randomisation: 2

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 one 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

Arm title	Monoclonal antibody (mAb) vedolizumab

Arm description:

Participants were scheduled to receive vedolizumab at weeks 2, 4, 8, 16, 24, and 32.

Arm type	Experimental
Investigational medicinal product name	Monoclonal antibody (mAb) 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 mls 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 30mls of normal saline. The mAb must be administered by healthcare professionals prepared to manage hypersensitivity.

Number of subjects in period 1	Monoclonal antibody (mAb) vedolizumab
Started	1
Completed	0
Not completed	1
Early termination of the trial	1

Baseline characteristics

End points

End points reporting groups

Reporting group title	Monoclonal antibody (mAb) vedolizumab
Reporting group description:	
Participants were scheduled to receive vedolizumab at weeks 2, 4, 8, 16, 24, and 32.	

Primary: Time from treatment interruption (scheduled for 24 weeks after entering the trial) to the earliest of reaching HIV RNA ≥ 10,000 copies/ml (confirmed on a separate sample) or resuming antiretroviral therapy for any reason over a period of 24 weeks

End point title	Time from treatment interruption (scheduled for 24 weeks after entering the trial) to the earliest of reaching HIV RNA ≥ 10,000 copies/ml (confirmed on a separate sample) or resuming antiretroviral therapy for any reason over a period of 24 weeks[1]
End point description:	

End point type	Primary
End point timeframe:	
Time from treatment interruption (scheduled for 24 weeks after entering the trial) to the earliest of reaching HIV RNA ≥ 10,000 copies/ml (confirmed on a separate sample) or resuming antiretroviral therapy for any reason over a period of 24 weeks	

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 before any investigational product administered.

End point values	Monoclonal antibody (mAb) vedolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Participants				

Notes:

[2] - Early termination of the trial

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
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	21.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Early termination of the trial before any investigational product administered.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2017	* Update to sections 6.7.1.D and 10 (plus tables 1 & 2) to further clarify sub-study procedures in countries other than UK and Italy * Trial summary updated with further details of treatment groups and distribution of active treatment and placebo. * Details on randomisation stages added to Trial summary and section 3.4. * Minor change to section 11.2: Word "component" was replaced by "approach". * A number of typos across the document were corrected.
12 December 2017	* Exclusion criteria updated to include personal and/or family history (parents and siblings) of clinical autoimmune disease or reactive arthritis * Sections 6.2, 6.4.1 and 6.7.1: Microbiome analysis will be done if the participant is willing and able to produce a stool sample, and the laboratory local to the clinic is able to process and store the sample at -80°C within 4 hours of the sample being produced. * Sections 6.2 and 10: Participants from France, Germany, Spain and Switzerland will be invited to take part in substudies, provided the local laboratories pass the quality control checks for sample processing and storage.
28 March 2018	* Section 5.6 Protocol treatment discontinuation: Participants who have received at least one injection or infusion will be asked to remain in the trial for the purpose of follow-up and data analysis at least until week 24 or for 4 weeks after the last trial intervention, whichever is the longest. * Section 5.10 Non-Trial Treatment: Participants will continue on their combination antiretroviral therapy through to week 24 when they will interrupt treatment provided it is safe to do so. Pregnancy added to the list of circumstances that may lead to resume cART. * Section 6.3.9 expanded. * Sections 6.4, 6.5 and 7.2.1: Notable events such as pregnancy may lead the Trial Safety Group to conclude that: * ART interruption is inadvisable * ART should be resumed * Interventional products will be discontinued * Section 6.7.1F Microbiome Study: Only sites where samples can be processed and stored at -80°C within 24 hours from being produced will participate and from participants who are willing and able to follow the procedures for collection. Exclusion of participants with chronic diarrhoea. * Section 7.2.1 Pregnancy: All pregnancies, including those occurring in female partners will be followed up to collect information about the outcome. * Section 8.1: Risks of exacerbation of recognised adverse events due to the combination of vaccines and vedolizumab and occurrence of new adverse events; Risk of disease progression following cART interruption and occurrence of progressive multifocal leukoencephalopathy (PML). * Sections 9.2 and 9.3 were created to describe the phase I and II components respectively. * Section 9.5 Interim Efficacy Stage: Changes made to "Time to interim analysis" and "Duration of the whole trial". * Sections 9.6 and 11.2.1 Ethical Considerations: IDMC will review the cumulative safety data after the 12th participant has had their first safety visit at week 1 or 4, before expanding recruitment. * Section 10 Ancillary/Substudies: clarification

13 September 2018	* Treatment(cART) will be resumed when CD4 T-cell count falls to ≤350cells/mm^3 confirmed * Introduction updated with more recent data on the global AIDS epidemic and updated information regarding cART benefit and toxicity. * Introduction and Risk Assessment updated with recent case of PML in HIV-positive individual. * Introduction updated with reference to a recent study of vedolizumab in HIV-positive individuals. * Table 5 footnote and 5.4.4 updated to clarify vaccine and infusion visit schedule. * Wording in 5.2.3 amended to be clear on what participants randomised to placebo should receive. * In 5.6 detailing protocol treatment discontinuation, one point regarding toxicity or adverse events has been reworded for clarity and a further point added about restarting cART. * An additional section was added to detail additional and more frequent pregnancy testing for women of childbearing potential throughout the trial. * 6.3.3 and 6.3.6 updated to include checklist of neurological symptoms associated with PML. * The procedures detailed in 6.5 now indicate that an Adverse Event assessment will take place at every follow-up visit. This section also adds that cART should be restarted in the case of pregnancy in a female participant, updates have been added to the wording around notable events and expedited reporting. * 10,000 copies/ml or more HIV RNA has been removed as a Notable Event from the list in 7.2. * The list of Notable Events now includes pregnancy. * 9.1 has been updated to explain that the randomisation of the first 12 participants will be restricted to chronic infection stratum. Clarification was also made in this section on the ratio between the four randomisation arms. * 9.5, Interim Safety Stage, has been added to detail a safety review to be performed when the 12th participant has their first safety visit following administration of product. * Table 9 has been updated. * A deletion was made to 9.8 with regard to primary outcome analysis.
06 December 2018	* Inclusion criteria - the CD4 T cell count at screening has been changed from > 600 cells/mm^3 to > 500 cells/mm^3 (trial summary and section 3.1 updated with this information). * Trial Assessment Schedule for Site Investigators (Table 1) - the visit windows have been updated to ±3 days for the early, more frequent visits, and a visit window of 0 days has been given where visits must occur according to the individual visit schedule. The footnote of Table 1 has also been amended accordingly. * In section 5.4.5 an error was corrected which referred to the MVA vaccine (or its placebo) being given at the same visit as an infusion (this will only be the DNA vaccine or its placebo). * SAE and Notable Event reporting has been clarified throughout in the text and in the blue boxes. SAEs, Notable Events and Pregnancy must be reported within 24 hours of the investigator becoming aware of the event. * Section 18 (Appendices) was updated to refer to the 'Participant' (rather than 'Patient') Information Sheets to match the appended documents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

06 March 2019	The clinical trial started only in Switzerland where only one participant was included without being administered a study product. Following the bankruptcy of FIT Biotech Oy, which develops and produces the GTU-MultiHIV clade B DNA vaccine used in the trial, and its inability to supply sufficient vaccine doses to complete the trial, a temporary halt was declared to the competent authority and the ethics committee of that country as soon as we became aware of the uncertainty regarding the supply of all the doses necessary to carry out the research. The Inserm-ANRS sponsor subsequently decided to proceed to an early termination of the EHVA T01/ANRS VRI05 clinical trial on 11 July 2019. As no products were administered in the trial, no results are available in this clinical trial.	-

Notes:

Limitations and caveats

None reported