Clinical trial results:
A Phase IIa, randomized, double-blind, placebo-controlled study of HIV-1 Vaccines MVA.HTI and ChAdOx1.HTI with TLR7 agonist vesatolimod (GS-9620) in early treated HIV-1 infection

Summary

EudraCT number	2018-002125-30
Trial protocol	ES
Global end of trial date	16 December 2022

Results information

Result version number	v1 (current)
This version publication date	12 August 2023
First version publication date	12 August 2023

Trial information

Trial identification

Sponsor protocol code	AELIX-003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AELIX Therapeutics
Sponsor organisation address	Parc Científic de Barcelona, C/ Baldiri i Reixac, 4-8, Barcelona, Spain, 08028
Public contact	Jordi Naval, AELIX Therapeutics, 34 934031339, jnaval@aelixtherapeutics.com
Scientific contact	Jordi Naval, AELIX Therapeutics, 34 934031339, jnaval@aelixtherapeutics.com

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	21 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2022
Global end of trial reached?	Yes
Global end of trial date	16 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of the CCMM (ChAdOx1.HTI + MVA.HTI) + Vesatolimod regimen during Period 1 (week 0 to 48) in early treated HIV 1 infection

Protection of trial subjects:

This study was conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, protocol, ICH harmonised tripartite guideline E6(R2): GCP, and all applicable AEMPS requirements. A written informed consent (including separate consent for the intensive PK substudy if applicable and potential updated or new information related to COVID 19, which could impact the study risk-benefit assessment) in compliance with AEMPS regulations was obtained from each participant.

Background therapy:

The most frequently taken concomitant medications (that were ongoing on or after the first dose of the IMP) were COVID-19 vaccines (31 [93.9%] participants in the CCMM + vesatolimod group and 17 [100%] participants in the placebo group), paracetamol (21 [63.6%] participants in the CCMM + vesatolimod group and 13 [76.5%] participants in the placebo group), and ibuprofen (16 [48.5%] participants in the CCMM + vesatolimod group and 7 [41.2%] participants in the placebo group).

Evidence for comparator:

Matching placebo

Actual start date of recruitment	20 May 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	Spain: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 57 participants were planned to be enrolled in the study. After providing informed consent, participants were randomly assigned in a 2:1 ratio using an IRT to receive CCMM + vesatolimod or placebo.

Pre-assignment

Screening details:

The study screened participants living with HIV who had initiated ART within 180 days (6 months) of the estimated date of HIV 1 acquisition and who had achieved virological suppression for at least 1 year. A total of 65 participants were assessed for eligibility and 50 participants enrolled in the study.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study treatments taken during this study were double-blind. Period 1 (48 weeks) during which participants received blinded investigational medicinal product (IMP) and continued their antiretroviral therapy (ART regimen).
Unblinded Roles: Pharmacist+ unblinded Study nurses, uCTM and uCRA

Arms

Are arms mutually exclusive?	Yes
Arm title	CCMM + Vesatolimod

Arm description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA). Vesatolimod (also known as GS-9620) is an orally administered toll-like receptor 7 (TLR7) agonist currently in clinical development for the treatment and remission of HIV-1 infection.

Arm type	Experimental
Investigational medicinal product name	ChAdOx1.HTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

ChAdOx1.HTI vaccine was delivered as one 0.5 mL IM injection, taken at Weeks 0 and 12.

Investigational medicinal product name	MVA.HTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MVA.HTI vaccine was delivered as one 0.5 mL IM injection, taken at Weeks 24 and 36.

Investigational medicinal product name	Vesatolimod
Investigational medicinal product code	
Other name	GS-9620
Pharmaceutical forms	Film-coated tablet

Routes of administration	Oral use

Dosage and administration details:

Vesatolimod was administered orally at the study site with approximately 240 mL of water after an overnight fast or after fasting period of at least 8 hours. Participants were not allowed to consume water 1 hour before and 2 hours after dosing. Vesatolimod was delivered as three 2-mg tablets and was taken at Weeks 26, 28, 30, 32, 34, 38, 40, 42, 44, and 46.

Arm title	Placebo

Arm description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Arm type	Placebo
Investigational medicinal product name	ChAdOx1.HTI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

ChAdOx1.HTI placebo (0.9% NaCl solution for injection) was delivered as one 0.5 mL IM injection and was taken at Weeks 0 and 12.

Investigational medicinal product name	MVA.HTI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

MVA.HTI (0.9% NaCl solution for injection) was delivered as one 0.5 mL IM injection and was taken at Weeks 24 and 36.

Investigational medicinal product name	Vesatolimod placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vesatolimod placebo was administered orally at the study site with approximately 240 mL of water after an overnight fast or after fasting period of at least 8 hours. Participants were not allowed to consume water 1 hour before and 2 hours after dosing. Vesatolimod placebo tablet was delivered as three 2-mg placebo tablets and was taken at Weeks 26, 28, 30, 32, 34, 38, 40, 42, 44, and 46.

Number of subjects in period 1	CCMM + Vesatolimod	Placebo
Started	33	17
Completed	30	17
Not completed	3	0
Withdrawal by participant	2	-
Investigator decision	1	-

Period 2

Period 2 title	Period 2 (ATI)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Participants were allowed to proceed to Period 2 if they met ATI requirements and had received at least 3 doses of vaccine/placebo and at least 3 doses of vesatolimod/placebo. During Period 2 (up to 24 weeks) participants discontinued their ART regimen (ATI period) and were monitored for pVL and CD4 counts.

Arms

Are arms mutually exclusive?	Yes
Arm title	CCMM + Vesatolimod

Arm description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA).

Arm type	Experimental
Investigational medicinal product name	ChAdOx1.HTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 2 (Week 48 to Week 72), all participants discontinued ART at/after the Week 48 visit. HIV-1 plasma viremia levels were monitored weekly and CD4 counts were monitored monthly. During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	MVA.HTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 2 (Week 48 to Week 72), all participants discontinued ART at/after the Week 48 visit. HIV-1 plasma viremia levels were monitored weekly and CD4 counts were monitored monthly. During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	Vesatolimod
Investigational medicinal product code	
Other name	GS-9620
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Period 2 (Week 48 to Week 72), all participants discontinued ART at/after the Week 48 visit. HIV-1 plasma viremia levels were monitored weekly and CD4 counts were monitored monthly. During this period subjects did not receive study drug/ placebo.

Arm title	Placebo

Arm description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Arm type	Placebo

Investigational medicinal product name	ChAdOx1.HTI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 2 (Week 48 to Week 72), all participants discontinued ART at/after the Week 48 visit. HIV-1 plasma viremia levels were monitored weekly and CD4 counts were monitored monthly. During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	MVA.HTI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 2 (Week 48 to Week 72), all participants discontinued ART at/after the Week 48 visit. HIV-1 plasma viremia levels were monitored weekly and CD4 counts were monitored monthly. During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	Vesatolimod placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Period 2 (Week 48 to Week 72), all participants discontinued ART at/after the Week 48 visit. HIV-1 plasma viremia levels were monitored weekly and CD4 counts were monitored monthly. During this period subjects did not receive study drug/ placebo.

Number of subjects in period 2	CCMM + Vesatolimod	Placebo
Started	30	17
Entered Period 2	30	17
Discontinued Period 2	0 [1]	0 [2]
Completed	30	17

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Three (9.1%) participants in the CCMM + vesatolimod group did not complete active treatment (Period 1). All participants who entered Period 2 completed the period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All participants in the placebo group completed active treatment (Period 1). All participants who entered Period 2 completed the period.

Period 3

Period 3 title	Period 3 (ART reinitiation)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Participants who met the requirements for restarting ART during Period 2 moved into Period 3 after restarting ART, whether during Period 2 or at the completion of Period 2 (i.e., at Week 72) underwent Week 72 procedures. During Period 3 (12 weeks) participants were monitored following the restart of their ART.

Arms

Are arms mutually exclusive?	Yes
Arm title	CCMM + Vesatolimod

Arm description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA).

Arm type	Experimental
Investigational medicinal product name	ChAdOx1.HTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 3 (Week 72 to Week 84), all participants who restarted their ART during Period 2, whether during Period 2 or after completing Period 2 (i.e., at the Week 72 visit), had their viral load monitored at 4 and 12 weeks after restarting ART (Week 76 and Week 84). During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	MVA.HTI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 3 (Week 72 to Week 84), all participants who restarted their ART during Period 2, whether during Period 2 or after completing Period 2 (i.e., at the Week 72 visit), had their viral load monitored at 4 and 12 weeks after restarting ART (Week 76 and Week 84). During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	Vesatolimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Period 3 (Week 72 to Week 84), all participants who restarted their ART during Period 2, whether during Period 2 or after completing Period 2 (i.e., at the Week 72 visit), had their viral load monitored at 4 and 12 weeks after restarting ART (Week 76 and Week 84). During this period subjects did not receive study drug/ placebo.

Arm title	Placebo

Arm description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Arm type	Placebo
Investigational medicinal product name	ChAdOx1.HTI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 3 (Week 72 to Week 84), all participants who restarted their ART during Period 2, whether during Period 2 or after completing Period 2 (i.e., at the Week 72 visit), had their viral load monitored at 4 and 12 weeks after restarting ART (Week 76 and Week 84). During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	MVA.HTI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In Period 3 (Week 72 to Week 84), all participants who restarted their ART during Period 2, whether during Period 2 or after completing Period 2 (i.e., at the Week 72 visit), had their viral load monitored at 4 and 12 weeks after restarting ART (Week 76 and Week 84). During this period subjects did not receive study drug/ placebo.

Investigational medicinal product name	Vesatolimod placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Period 3 (Week 72 to Week 84), all participants who restarted their ART during Period 2, whether during Period 2 or after completing Period 2 (i.e., at the Week 72 visit), had their viral load monitored at 4 and 12 weeks after restarting ART (Week 76 and Week 84). During this period subjects did not receive study drug/ placebo.

Number of subjects in period 3	CCMM + Vesatolimod	Placebo
Started	30	17
Enter Period 3	30	17
Discontinued Period 3	0 [3]	1 [4]
Completed the Study	30	16
Completed	30	16
Not completed	0	1
Withdrawal by participant	-	1

Notes:

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All participants who entered Period 3 completed the study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only 1 (5.9%) participant in the placebo group discontinued from the study during Period 3 due to withdrawal by participant.

Baseline characteristics

Reporting groups	
Reporting group title	CCMM + Vesatolimod
Reporting group description:	
ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA). Vesatolimod (also known as GS-9620) is an orally administered toll-like receptor 7 (TLR7) agonist currently in clinical development for the treatment and remission of HIV-1 infection.	
Reporting group title	Placebo
Reporting group description:	
The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).	

Reporting group values	CCMM + Vesatolimod	Placebo	Total
Number of subjects	33	17	50
Age categorical			
Units: Subjects			
Adults (18-64 years)	33	17	50
Age continuous			
Units: years			
arithmetic mean	38.4	36.8	
standard deviation	± 8.77	± 12.42	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	33	17	50
HLA with potential for superior viral control (Corrected)			
Baseline was defined as the last nonmissing assessment prior to the first administration of any IMP. A total of 10 (20.0%) participants (6 [18.2%] in the CCMM + vesatolimod group and 4 [23.5%] in the placebo group) had potential for superior viral control due to the presence of human leukocyte antigen (HLA allele(s)) associated with natural control of HIV. Median time since HIV acquisition to screening visit was 43.08 months (41.79 months in the CCMM + vesatolimod group and 46.45 months in the placebo group).			
Units: Subjects			
Yes	6	4	10
No	27	13	40
Time from HIV acquisition to ART initiation			
Time from HIV acquisition to ART initiation = the ART initiation date — the estimated date of HIV-1 acquisition.			
Units: days			
median	61.0	86.0	
full range (min-max)	7 to 170	16 to 167	-

Subject analysis sets	
Subject analysis set title	ITT set
Subject analysis set type	Full analysis

Subject analysis set description:

ITT set was defined as all randomized participants who took at least one dose of IMP. Numbers were based on planned treatment group.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety set was defined as all randomized participants who took at least one dose of IMP. Numbers were based on actual treatment group.

Reporting group values	ITT set	Safety set	
Number of subjects	50	50	
Age categorical Units: Subjects			
Adults (18-64 years)	17	33	
Age continuous Units: years			
arithmetic mean	37.9	37.9	
standard deviation	± 10.06	± 10.06	
Gender categorical Units: Subjects			
Female	0	0	
Male	50	50	
HLA with potential for superior viral control (Corrected)			
Baseline was defined as the last nonmissing assessment prior to the first administration of any IMP. A total of 10 (20.0%) participants (6 [18.2%] in the CCMM + vesatolimod group and 4 [23.5%] in the placebo group) had potential for superior viral control due to the presence of human leukocyte antigen (HLA allele(s)) associated with natural control of HIV. Median time since HIV acquisition to screening visit was 43.08 months (41.79 months in the CCMM + vesatolimod group and 46.45 months in the placebo group).			
Units: Subjects			
Yes	10	10	
No	40	40	
Time from HIV acquisition to ART initiation			
Time from HIV acquisition to ART initiation = the ART initiation date — the estimated date of HIV-1 acquisition.			
Units: days			
median	67.0	67.0	
full range (min-max)	7 to 170	7 to 170	

End points

End points reporting groups

Reporting group title	CCMM + Vesatolimod

Reporting group description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA). Vesatolimod (also known as GS-9620) is an orally administered toll-like receptor 7 (TLR7) agonist currently in clinical development for the treatment and remission of HIV-1 infection.

Reporting group title	Placebo

Reporting group description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Reporting group title	CCMM + Vesatolimod

Reporting group description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA).

Reporting group title	Placebo

Reporting group description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Reporting group title	CCMM + Vesatolimod

Reporting group description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA).

Reporting group title	Placebo

Reporting group description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Subject analysis set title	ITT set
Subject analysis set type	Full analysis

Subject analysis set description:

ITT set was defined as all randomized participants who took at least one dose of IMP. Numbers were based on planned treatment group.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety set was defined as all randomized participants who took at least one dose of IMP. Numbers were based on actual treatment group.

Primary: Proportion of participants who developed solicited Grade 3 or 4 local reactions in the 7-day period following administration of IMPs during Period 1

End point title	Proportion of participants who developed solicited Grade 3 or 4 local reactions in the 7-day period following administration of IMPs during Period 1[1]

End point description:

The incidence of Grade 3 or 4 solicited local reactions in the CCMM + vesatolimod group was higher than in the placebo group. 95% CI of the proportion was calculated based on the exact method and was (5.1, 31.9) for CCMM + vesatolimod group and (0.0, 19.5) for placebo group.
Diary event severity was assessed by the participant. AE severity was assessed by the investigator, Grade 1 was presented as 'Mild', Grade 2 was presented as 'Moderate'; Grade 3,4 or death were presented as 'Severe'.

End point type	Primary

End point timeframe:

From administration of IMP within the 7 days following IMP dosing (during Period 1)

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: No statistical analyses have been provided for safety end points since data was summarized using descriptive statistics.

End point values	CCMM + Vesatolimod	Placebo	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	17	50	
Units: number of subjects				
Grade 3	5	0	5	
Grade 4	1	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of participants who developed solicited Grade 3 or 4 systemic reactions in the 7-day period following administration of IMPs during Period 1

End point title	Proportion of participants who developed solicited Grade 3 or 4 systemic reactions in the 7-day period following administration of IMPs during Period 1[2]

End point description:

The incidence of Grade 3 solicited systemic reactions in the CCMM + vesatolimod group was higher than in the placebo group, whereas all Grade 4 solicited systemic reactions were reported in the placebo group. Ten (30.3%) participants in the CCMM + vesatolimod group had 40 and 3 (17.6%) participants in the placebo group had twenty Grade 3 solicited systemic reactions during Period 1. 95% CI of the proportion was calculated based on the exact method and was (15.6, 48.7) for CCMM + vesatolimod group and (3.8, 43.4) for placebo group.
Diary event severity is assessed by the participant. AE severity was assessed by the investigator, Grade 1 was presented as 'Mild', Grade 2 was presented as 'Moderate'; Grade 3,4 or death were presented as 'Severe'.

End point type	Primary

End point timeframe:

From administration of IMP within the 7 days following IMP dosing (during Period 1)

Notes:

[2] - 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: No statistical analyses have been provided for safety end points since data was summarized using descriptive statistics.

End point values	CCMM + Vesatolimod	Placebo	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	17	50	
Units: number of subjects				
Grade 3	10	3	13	
Grade 4	0	2	2	

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of participants who developed treatment-emergent SAEs during Period 1

End point title	Proportion of participants who developed treatment-emergent SAEs during Period 1[3]

End point description:

The serious TEAE was considered severe and was reported as recovered/resolved. The median duration for the serious TEAE during Period 1 was 10 days (range: 10.0 to 10.0). It was considered not related to the IMP.

End point type	Primary

End point timeframe:

From administration of IMP up to 48 weeks (during Period 1)

Notes:

[3] - 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: No statistical analyses have been provided for safety end points since data was summarized using descriptive statistics.

End point values	CCMM + Vesatolimod	Placebo	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	17	50	
Units: subjects				
number (confidence interval 95%)	1 (0.1 to 15.8)	0 (0 to 19.5)	1 (0.1 to 10.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (including SAEs) would be collected beginning from the time the participant signs the ICF and until the completion of the study.

Adverse event reporting additional description:

ChAdOx1.HTI, MVA.HTI, and vesatolimod were found to be generally safe and well-tolerated, no new safety signal detected.
A TEAE is defined as any event not present before exposure to IMP or any event already present that worsens in either intensity or frequency after exposure to IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	CCMM + Vesatolimod

Reporting group description:

ChAdOx1.HTI is an immunotherapeutic medicinal product that contains genetically modified organisms (ChAdOx1). MVA.HTI is an investigational immunological product (vaccine) of a biological/biotechnological origin that contains genetically modified organisms (MVA). Vesatolimod (also known as GS-9620) is an orally administered toll-like receptor 7 (TLR7) agonist currently in clinical development for the treatment and remission of HIV-1 infection.

Reporting group title	Placebo

Reporting group description:

The placebos matched to ChAdOx1.HTI and MVA.HTI were commercially available sterile saline solution (sodium chloride 0.9%).

Serious adverse events	CCMM + Vesatolimod	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	0 / 17 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CCMM + Vesatolimod	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	32 / 33 (96.97%)	17 / 17 (100.00%)	
Vascular disorders Varicose vein subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 17 (5.88%) 1	
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all)	29 / 33 (87.88%) 64	5 / 17 (29.41%) 9	
Influenza like illness subjects affected / exposed occurrences (all)	12 / 33 (36.36%) 40	4 / 17 (23.53%) 5	
Fatigue subjects affected / exposed occurrences (all)	11 / 33 (33.33%) 17	4 / 17 (23.53%) 17	
Asthenia subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 11	5 / 17 (29.41%) 12	
Injection site induration subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 10	2 / 17 (11.76%) 3	
Injection site erythema subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	2 / 17 (11.76%) 3	
Malaise subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 7	1 / 17 (5.88%) 1	
Pyrexia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 5	2 / 17 (11.76%) 2	
Chills subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 17 (5.88%) 3	
Injection site reaction			

subjects affected / exposed	3 / 33 (9.09%)	1 / 17 (5.88%)	
occurrences (all)	5	1	
Injection site pruritus			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Vaccination site pain			
subjects affected / exposed	0 / 33 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Injection site bruising			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injection site warmth			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	5 / 33 (15.15%)	6 / 17 (35.29%)	
occurrences (all)	16	9	
Cough			
subjects affected / exposed	3 / 33 (9.09%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Rhinorrhoea			
subjects affected / exposed	0 / 33 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 33 (9.09%)	4 / 17 (23.53%)	
occurrences (all)	3	4	
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Affective disorder			

subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Substance abuse			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Investigations			
Mycoplasma test positive			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 33 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Vaccination complication			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Limb injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Penis injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 33 (48.48%)	10 / 17 (58.82%)	
occurrences (all)	38	21	
Tension headache			
subjects affected / exposed	1 / 33 (3.03%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Dizziness			
subjects affected / exposed	2 / 33 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Migraine with aura			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Myoclonus			

subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	3 / 33 (9.09%)	3 / 17 (17.65%)	
occurrences (all)	3	4	
Lymph node pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Photopsia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 33 (18.18%)	6 / 17 (35.29%)	
occurrences (all)	6	11	
Diarrhoea			
subjects affected / exposed	5 / 33 (15.15%)	6 / 17 (35.29%)	
occurrences (all)	6	7	
Abdominal pain			
subjects affected / exposed	3 / 33 (9.09%)	2 / 17 (11.76%)	
occurrences (all)	4	2	
Proctalgia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Dyspepsia			

subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Haemorrhoids			
subjects affected / exposed	0 / 33 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Toothache			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 33 (6.06%)	2 / 17 (11.76%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 33 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 33 (33.33%)	1 / 17 (5.88%)	
occurrences (all)	12	3	
Myalgia			
subjects affected / exposed	9 / 33 (27.27%)	2 / 17 (11.76%)	
occurrences (all)	12	4	
Back pain			
subjects affected / exposed	4 / 33 (12.12%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
Muscle spasms			

subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 33 (27.27%)	7 / 17 (41.18%)	
occurrences (all)	9	7	
Upper respiratory tract infection			
subjects affected / exposed	6 / 33 (18.18%)	4 / 17 (23.53%)	
occurrences (all)	6	5	
Nasopharyngitis			
subjects affected / exposed	5 / 33 (15.15%)	2 / 17 (11.76%)	
occurrences (all)	7	3	
Syphilis			
subjects affected / exposed	3 / 33 (9.09%)	2 / 17 (11.76%)	
occurrences (all)	3	2	
Proctitis gonococcal			
subjects affected / exposed	2 / 33 (6.06%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Tonsillitis			
subjects affected / exposed	1 / 33 (3.03%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Bronchitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	2	0	

Folliculitis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Hordeolum			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Oral herpes			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Oropharyngeal gonococcal infection			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Pharyngeal chlamydia infection			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Tinea versicolour			
subjects affected / exposed	1 / 33 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Urethritis gonococcal			
subjects affected / exposed	2 / 33 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Furuncle			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastroenteritis shigella			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Genital herpes simplex			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gonorrhoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Latent syphilis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Oral candidiasis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Proctitis chlamydial			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Ureaplasma infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 33 (9.09%)	3 / 17 (17.65%)	
occurrences (all)	5	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2019	The following is a summary of the major changes implemented with Protocol Amendment 2 (substantial), dated 07 Oct 2019: • The vesatolimod dose was reduced from 8 mg to 6 mg and study monitoring plan following the first dose of vesatolimod and subsequent doses was updated to include a 24-hour on-site admission period following the first dose and an 8-hour observation period following subsequent doses to monitor for CRS. • The study was simplified by removing the GALT substudy, eliminating 2 treatment arms (and reducing the number of participants), and eliminating the sentinel dosing cohort (based on safety data from another study). • The size of intensive PK substudy was reduced from 18 to 15 participants. • The number of participants was changed to 57 (38 in the CCMM + vesatolimod group and 19 in the placebo group). • The randomization stratification by sentinel and non-sentinel cohorts was removed. • Stratification based on the potential for superior viral control (based on HLA genotype) was added.
24 September 2020	The following is a summary of the major changes implemented with Protocol Amendment 4 (substantial), dated 24 Sep 2020: • Text was added to introduce the conduct of the study during the COVID-19 pandemic, including the benefit-risk assessment of ChAdOx1. HTI, MVA.HTI, and vesatolimod, and the measures taken during the COVID-19 pandemic, such as SARS CoV 2 PCR, serological tests, and remote visits in relation to vesatolimod/placebo administration and certain non-IMP dosing visits. • Safety data of the relevant clinical studies on the study vaccines were updated based on the latest DSUR, dated on 08 Apr 2020.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported