



Clinical trial results:

RIVER - Research In Viral Eradication of HIV Reservoirs, A two-arm (proof of concept) randomised phase II trial

Summary

EudraCT number	2014-001425-32
Trial protocol	GB
Global end of trial date	31 March 2023

Results information

Result version number	v1 (current)
This version publication date	12 April 2024
First version publication date	12 April 2024

Trial information

Trial identification

Sponsor protocol code	14SM2359
-----------------------	----------

Additional study identifiers

ISRCTN number	ISRCTN83717528
ClinicalTrials.gov id (NCT number)	NCT02336074
WHO universal trial number (UTN)	U1111-1163-2579
Other trial identifiers	Sponsor Reference: 14SM2359

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington, London, United Kingdom, SW7 2AZ
Public contact	RIVER Trial Manager, MRC Clinical Trial Unit at UCL, 0044 0207 670 4773, mrcctu.river@ucl.ac.uk
Scientific contact	RIVER Trial Manager, MRC Clinical Trial Unit at UCL, 0044 0207 670 4773, mrcctu.river@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	14 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2017
Global end of trial reached?	Yes
Global end of trial date	31 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To see whether in primary HIV infection, a combination of immediate combination ART (cART), immunisation and latency reactivation using the HDACi vorinostat will confer a significant reduction in the HIV reservoir when compared with cART alone.

Protection of trial subjects:

Initiation of immediate ART for individuals with PHI is within routine practice within the UK.

The vaccine strategy has been given to HIV uninfected individuals and is safe and well tolerated.

There is an unknown long-term risk of toxicity following use of vorinostat. The steps taken to minimise risk and safeguard patients include:

- 1) very stringent inclusion and exclusion criteria to avoid enrolment of patients in which the receipt of vorinostat would cause an increased risk (theoretical or proven) of harm, for example we exclude anyone with a past history of cancer;
- 2) close monitoring (safety bloods and clinical assessment) during the study in order to manage and minimise side effects. Clear dose reduction and stopping rules within the protocol during vorinostat dosing;
- 3) exclusion of women of child bearing potential as in preclinical studies, vorinostat caused chromosomal rearrangement in the hamster ovary.
- 4) Long term annual follow-up for 5 years after completion of the study.
- 5) men with female partners must avoid getting their partners pregnant for 6 months of the intervention.

Additional inclusion criteria (including safety bloods, ECG and urinalysis) have to be met before the patient is randomised at week 24, and before receipt of vorinostat at week 32 Day 3.

All research staff involved in the conduct of the study at the sites are very experienced, including several in HIV vaccine studies.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	60
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)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

82 participants were screened at 6 clinical centres in the UK of whom 63 were enrolled, 3 withdrew before randomisation, and 60 participants were randomised between 14 Jun 2016 - 11 Jul 2017: 30 control and 30 intervention.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	82 ^[1]
Intermediate milestone: Number of subjects	Enrolment: 63
Number of subjects completed	60

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Prolonged QTc interval: 5
Reason: Number of subjects	Concurrent comorbidity: 2
Reason: Number of subjects	PHI diagnosis more than 4 weeks ago: 3
Reason: Number of subjects	Laboratory abnormalities: 5
Reason: Number of subjects	Patient decision: 1
Reason: Number of subjects	Contraindication vorinostat + QTc interval: 1
Reason: Number of subjects	Contraindication for vaccines: 1
Reason: Number of subjects	PHI diagnosis >4 weeks ago + QTc interval: 1
Reason: Number of subjects	Post enrolment: withdrawn/lost: 3

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: 82 individuals were screened at 6 sites in the UK of whom 63, aged 18–60 years who fulfilled all other eligibility criteria were enrolled in the study. ART was initiated at enrolment and randomisation occurred 24 weeks later, provided that the plasma HIV RNA was less than 50 copies per ml. Three of 63 participants withdrew before randomisation, and 60 were randomised. Not all patients screened have been enrolled.

Period 1

Period 1 title	Main study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A, Control

Arm description:

Active Comparator: Control

Combination Antiretroviral Therapy (cART) preferably including raltegravir prescribed at week 0 for the duration of the study up to post-randomisation week 18 (42 weeks in total)

Arm type	Active comparator
----------	-------------------

Investigational medicinal product name	Combination Antiretroviral Therapy (cART)
Investigational medicinal product code	
Other name	Truvada, Darunavir, Ritonavir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

cART is prescribed at enrolment/randomisation for the duration of the study.

Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	Isentress
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Raltegravir dosage: oral 400mg tablet twice per day (BID).

Arm title	Arm B, Intervention
------------------	---------------------

Arm description:

Experimental: Intervention

Combination Antiretroviral Therapy (cART) preferably including raltegravir prescribed at week 0 for the duration of the study up to post-randomisation week 18 (42 weeks in total) Plus ChAdV63.HIVconsV prime (post-randomisation week 00) and MVA.HIVconsV boost (post randomisation week 08 day 1) vaccines; followed by a 28-day course of vorinostat (10 doses in total).

Arm type	Experimental
Investigational medicinal product name	Combination Antiretroviral Therapy (cART)
Investigational medicinal product code	
Other name	Truvada, Darunavir, Ritonavir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

cART is prescribed at enrolment/randomisation for the duration of the study.

Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	Isentress
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Raltegravir dosage: oral 400mg tablet twice per day (BID).

Investigational medicinal product name	Vorinostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vorinostat (suberoylanilide hydroxamic acid abbreviated to SAHA) inhibits the histone deacetylases HDAC1, HDAC2, HDAC3 (Class I) and HDAC6 (Class II).

Vorinostat is supplied as capsules containing 100mg vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate.

Dosage: oral 400mg every third day from post randomisation week 8 day 3 (PR08-3) to week 12 day 2 (PR12-2) inclusive. 10 doses in total.

Administration: Vorinostat is administered orally with food. Participants should drink at least 2L fluid/day (on drug dosing days) to prevent dehydration and must report any excessive vomiting or diarrhoea; signs or symptoms of deep vein thrombosis (swelling and pain in a limb, shortness of breath, cough, pleuritic chest pain); unusual bleeding and seek medical attention.

Investigational medicinal product name	ChAdV63.HIVconsV (ChAd)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage: 5×10^{10} vp

Administration: This dose is obtained by injecting 0.37ml of the vaccine at 1.35×10^{11} vp/ml without dilution. This prime vaccination is administered intramuscularly (IM) into the deltoid muscle of the non-dominant arm within 1 week of randomisation at visit post randomisation week 00 (PR00).

Investigational medicinal product name	MVA.HIVconsV (MVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage: 2×10^8 pfu

Administration: This dose is obtained by injecting 0.23 ml of the vaccine IM at 8.6×10^8 pfu/ml without dilution. This boost vaccination is administered intramuscularly (IM) into the deltoid muscle of the non-dominant arm at post-randomisation week 08 Day 1 (2 prior to start of vorinostat)

Number of subjects in period 1	Arm A, Control	Arm B, Intervention
Started	30	30
Completed	30	30

Baseline characteristics

Reporting groups

Reporting group title	Arm A, Control
Reporting group description:	
Active Comparator: Control	
Combination Antiretroviral Therapy (cART) preferably including raltegravir prescribed at week 0 for the duration of the study up to post-randomisation week 18 (42 weeks in total)	
Reporting group title	Arm B, Intervention
Reporting group description:	
Experimental: Intervention	
Combination Antiretroviral Therapy (cART) preferably including raltegravir prescribed at week 0 for the duration of the study up to post-randomisation week 18 (42 weeks in total) Plus ChAdV63.HIVconsV prime (post-randomisation week 00) and MVA.HIVconsV boost (post randomisation week 08 day 1) vaccines; followed by a 28-day course of vorinostat (10 doses in total).	

Reporting group values	Arm A, Control	Arm B, Intervention	Total
Number of subjects	30	30	60
Age categorical			
Aged ≥18 to ≤60 years old			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	30	60
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	31	35	
inter-quartile range (Q1-Q3)	30 to 38	28 to 44	-
Gender categorical			
All 60 participants were male			
Units: Subjects			
Female	0	0	0
Male	30	30	60
Stratum			
Units: Subjects			
Stratum 1	26	26	52
Stratum 2	4	4	8
Ethnicity			
Units: Subjects			
White	16	26	42
South Asian	0	1	1
South East Asian	1	0	1
Hispanic/Latino	3	2	5

Black Caribbean/American	2	0	2
Black African	2	0	2
Mixed ethnic group	5	1	6
Other	1	0	1
Mode of HIV infection			
Units: Subjects			
MSM	26	29	55
MSW	1	1	2
Unknown	1	0	1
MSM+IDU	2	0	2
HIV RNA			
Units: Subjects			
<50 copies/ml	29	30	59
50 - <200 copies/ml	1	0	1
Weeks since PHI diagnosis			
Units: Subjects			
≤1 week	1	0	1
>1 - 2 weeks	3	3	6
>2 - 3 weeks	7	7	14
>3 - 4 weeks	15	16	31
>4 weeks	4	4	8
CD4 cell count			
Units: cells/mm ³			
median	694	710	
inter-quartile range (Q1-Q3)	561 to 844	579 to 759	-
CD4/CD8 ratio			
Units: ratio			
median	1.09	1.07	
inter-quartile range (Q1-Q3)	0.77 to 1.42	0.91 to 1.46	-
eGFR			
Units: mL/min/1.73 m ²			
median	106	111	
inter-quartile range (Q1-Q3)	99 to 119	105 to 120	-
Time since PHI diagnosis			
Units: weeks			
median	28	28	
inter-quartile range (Q1-Q3)	27 to 41	27 to 34	-

End points

End points reporting groups

Reporting group title	Arm A, Control
Reporting group description:	
Active Comparator: Control	
Combination Antiretroviral Therapy (cART) preferably including raltegravir prescribed at week 0 for the duration of the study up to post-randomisation week 18 (42 weeks in total)	
Reporting group title	Arm B, Intervention
Reporting group description:	
Experimental: Intervention	
Combination Antiretroviral Therapy (cART) preferably including raltegravir prescribed at week 0 for the duration of the study up to post-randomisation week 18 (42 weeks in total) Plus ChAdV63.HIVconsv prime (post-randomisation week 00) and MVA.HIVconsv boost (post randomisation week 08 day 1) vaccines; followed by a 28-day course of vorinostat (10 doses in total).	

Primary: Total HIV DNA from CD4 T-cells averaged across post randomisation weeks 16 and 18

End point title	Total HIV DNA from CD4 T-cells averaged across post randomisation weeks 16 and 18
End point description:	
<p>The primary endpoint was total HIV-DNA averaged across post-randomisation weeks 16 and 18. It was analysed on a log10-scale. Treatment arms were compared in terms of absolute total HIV DNA levels at post-randomisation weeks 16 and 18 adjusted for the baseline (i.e. randomisation) level and by stratum using analysis of covariance.</p> <p>If either the PR week 16 result or the PR week 18 result were entirely missing but not both, the primary endpoint consisted of the single available result. If total HIV DNA was missing at both PR-16 or PR-18, or at baseline, an imputation method was used to estimate missing values. Predictors included stratum, total HIV-DNA from previous time-points and other factors associated with total HIV DNA."</p> <p>Baseline results were missing in 2 participants. Results were imputed using stratum and mean total HIV-DNA from PR week 16 and 18. Therefore, the primary analysis of the primary endpoint included all 60 randomised participants.</p>	
End point type	Primary
End point timeframe:	
Post randomisation weeks 16 and 18	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: HIV-DNA copies/million CD4+T cells				
log mean (standard deviation)	2.95 (± 0.50)	3.06 (± 0.49)		

Statistical analyses

Statistical analysis title	Difference in total HIV-DNA
Statistical analysis description: Difference: Intervention minus Control. Analysis using linear regression on log10 scale adjusted for baseline value and stratum	
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.256
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.036

Secondary: Integrated HIV DNA from CD4 T-cells averaged across post randomisation weeks 16 and 18

End point title	Integrated HIV DNA from CD4 T-cells averaged across post randomisation weeks 16 and 18
End point description:	
End point type	Secondary
End point timeframe: Post randomisation weeks 16 and 18	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	23		
Units: copies per 10 CD4+ T cells				
log mean (standard deviation)	2.79 (± 0.51)	2.83 (± 0.45)		

Statistical analyses

Statistical analysis title	Difference
Statistical analysis description: Difference: Intervention minus Control. Derived from linear regression adjusted for baseline value and stratum on log10 scale	
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Viral outgrowth (replication competence)

End point title	Viral outgrowth (replication competence)
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 16	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	27		
Units: undetectable viral outgrowth	12	6		

Statistical analyses

Statistical analysis title	Difference
Statistical analysis description:	
Logistic regression, adjusted for stratum & baseline undetectable and imputed missing baseline results (imputed separately for each arm using multiple imputation based on stratum and PR week 16 results). Control in the model: Arm A	
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.145
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: HIV RNA from single copy assay

End point title	HIV RNA from single copy assay
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 18	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	29		
Units: copies/mL				
median (inter-quartile range (Q1-Q3))	6 (1 to 20)	6 (1 to 14)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV cell-associated unspliced RNA

End point title	HIV cell-associated unspliced RNA
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 16 and 18, average	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	23		
Units: copies per ng				
median (inter-quartile range (Q1-Q3))	0.12 (0.02 to 0.90)	0.29 (0.01 to 0.96)		

Statistical analyses

Statistical analysis title	Difference in HIV cell associated RNA
Statistical analysis description: Median regression of post-randomisation weeks 16 & 18 average, with bootstrapped standard error (Stata command bsqreg), adjusted for baseline value and stratum, to estimate the difference Intervention minus Control.	
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Median regression
Parameter estimate	Median difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.11

Secondary: HIV-specific CD4+ T cells positive for CD154

End point title	HIV-specific CD4+ T cells positive for CD154
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.021 (0.001 to 0.037)	0.141 (0.065 to 0.256)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for CD154

End point title	HIV-specific CD4+ T cells positive for CD154
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.025 (0.011 to 0.049)	0.174 (0.118 to 0.257)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for IFN γ

End point title	HIV-specific CD4+ T cells positive for IFN γ
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.007 (0.000 to 0.042)	0.102 (0.051 to 0.235)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for IFN γ

End point title	HIV-specific CD4+ T cells positive for IFN γ
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.034 (0.007 to 0.061)	0.181 (0.070 to 0.266)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for IL2

End point title	HIV-specific CD4+ T cells positive for IL2
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.006 (0.000 to 0.024)	0.073 (0.022 to 0.132)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for IL2

End point title	HIV-specific CD4+ T cells positive for IL2
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.008 (0.000 to 0.019)	0.118 (0.069 to 0.158)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for TNFa

End point title	HIV-specific CD4+ T cells positive for TNFa
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.020 (0.002 to 0.051)	0.183 (0.104 to 0.274)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD4+ T cells positive for TNFα

End point title	HIV-specific CD4+ T cells positive for TNFα
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.028 (0.011 to 0.059)	0.175 (0.128 to 0.300)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for CD154

End point title	HIV-specific CD8+ T cells positive for CD154
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.008 (0.000 to 0.017)	0.011 (0.006 to 0.036)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for CD154

End point title	HIV-specific CD8+ T cells positive for CD154
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.004 (0.000 to 0.010)	0.009 (0.002 to 0.040)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for IFN γ

End point title	HIV-specific CD8+ T cells positive for IFN γ
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.114 (0.036 to 0.307)	0.320 (0.195 to 0.942)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for IFN γ

End point title	HIV-specific CD8+ T cells positive for IFN γ
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.170 (0.057 to 0.279)	0.309 (0.177 to 1.061)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for IL2

End point title	HIV-specific CD8+ T cells positive for IL2
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.004 (0.000 to 0.015)	0.065 (0.010 to 0.190)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for IL2

End point title	HIV-specific CD8+ T cells positive for IL2
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.010 (0.000 to 0.032)	0.017 (0.000 to 0.105)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for TNFa

End point title	HIV-specific CD8+ T cells positive for TNFa
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.104 (0.033 to 0.207)	0.240 (0.102 to 0.645)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Wilcoxon (Mann-Whitney)

Secondary: HIV-specific CD8+ T cells positive for TNFa

End point title	HIV-specific CD8+ T cells positive for TNFa
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: proportion of cells				
median (inter-quartile range (Q1-Q3))	0.139 (0.018 to 0.255)	0.232 (0.102 to 0.585)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Wilcoxon (Mann-Whitney)

Secondary: CD8+ T Cell antiviral activity (viral inhibition)

End point title	CD8+ T Cell antiviral activity (viral inhibition)
End point description:	
CD8+ T cell antiviral suppressive activity will be expressed as percentage inhibition and determined as follows: $[(\text{fraction of p24 + cells in CD4 + T cells cultured alone}) - (\text{fraction of p24 + in CD4+ T cells cultured with CD8+ cells})] / (\text{fraction of p24 + cells in CD4 + T cells cultured alone}) \times 100$. A CD4:CD8 ratio of 10:1 was used for this analysis.	
End point type	Secondary
End point timeframe:	
Post randomisation week 9	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: % inhibition				
median (inter-quartile range (Q1-Q3))	41 (11 to 86)	75 (22 to 95)		

Statistical analyses

Statistical analysis title	Difference in change from randomisation
Statistical analysis description: Linear regression, adjusted for baseline result and stratum Difference between arms defined as Intervention minus Control	
Comparison groups	Arm B, Intervention v Arm A, Control
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	14.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	31.64
Variability estimate	Standard error of the mean
Dispersion value	8.61

Secondary: CD8+ T Cell antiviral activity (viral inhibition)

End point title	CD8+ T Cell antiviral activity (viral inhibition)
End point description: CD8+ T cell antiviral suppressive activity will be expressed as percentage inhibition and determined as follows: [(fraction of p24 + cells in CD4 + T cells cultured alone)– (fraction of p24 + in CD4+ T cells cultured with CD8+ cells)]/(fraction of p24 + cells in CD4 +T cells cultured alone) × 100. A CD4:CD8 ratio of 10:1 was used for this analysis.	
End point type	Secondary
End point timeframe: Post randomisation week 12	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: % inhibition				
median (inter-quartile range (Q1-Q3))	21 (4 to 65)	71 (14 to 92)		

Statistical analyses

Statistical analysis title	Difference in change from randomisation
Statistical analysis description: linear regression, adjusted for baseline result and stratum. Difference between arms defined as Intervention minus Control	
Comparison groups	Arm A, Control v Arm B, Intervention

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	19.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.42
upper limit	37.08
Variability estimate	Standard error of the mean
Dispersion value	8.61

Secondary: CD4/CD8 ratio

End point title	CD4/CD8 ratio
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 8	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: ratio				
median (inter-quartile range (Q1-Q3))	1.08 (0.84 to 1.41)	1.16 (0.82 to 1.42)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	t-test, 2-sided

Secondary: CD4/CD8 ratio

End point title	CD4/CD8 ratio
End point description:	
End point type	Secondary
End point timeframe:	
Post randomisation week 16	

End point values	Arm A, Control	Arm B, Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: ratio				
median (inter-quartile range (Q1-Q3))	1.18 (0.89 to 1.53)	1.27 (0.93 to 1.50)		

Statistical analyses

Statistical analysis title	Difference
Comparison groups	Arm A, Control v Arm B, Intervention
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main trial: randomisation to post randomisation week 18.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19
--------------------	----

Reporting groups

Reporting group title	Control
-----------------------	---------

Reporting group description: -

Reporting group title	Intervention
-----------------------	--------------

Reporting group description: -

Serious adverse events	Control	Intervention	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Syncope vasovagal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control	Intervention	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 30 (73.33%)	29 / 30 (96.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Tags			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Administration Site Rash			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Excessive Thirst			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 30 (0.00%)	11 / 30 (36.67%)	
occurrences (all)	0	11	
Flu-Like Symptoms			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
General Malaise			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Injection Site Muscle Pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Injection Site Pain			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Night Sweats			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Tiredness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vaccination Site Induration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vaccination Site Pain			
subjects affected / exposed	0 / 30 (0.00%)	5 / 30 (16.67%)	
occurrences (all)	0	6	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Hay Fever			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Nasal Congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Sore Throat			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Low Mood			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Panic Attack			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vivid Dreams			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Head Injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Insect Bite Nos			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Soft Tissue Injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Wrist Injury			

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Cardiac disorders Atrioventricular Block subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Forgetfulness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Light Headedness subjects affected / exposed occurrences (all) Sleepiness subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0 1 / 30 (3.33%) 1 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0	1 / 30 (3.33%) 1 0 / 30 (0.00%) 0 4 / 30 (13.33%) 4 1 / 30 (3.33%) 1 2 / 30 (6.67%) 3	
Gastrointestinal disorders Acute Gastroenteritis subjects affected / exposed occurrences (all) Anal Fissure subjects affected / exposed occurrences (all) Anal Warts subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 0 / 30 (0.00%) 0	0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 1 / 30 (3.33%) 1	

subjects affected / exposed	3 / 30 (10.00%)	7 / 30 (23.33%)	
occurrences (all)	3	9	
Dry Mouth			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Epigastric Pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Heartburn			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Loose Stools			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	0 / 30 (0.00%)	5 / 30 (16.67%)	
occurrences (all)	0	5	
Proctitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Rectal Bleeding			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Epidermal Cyst			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Erythematous Rash			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Folliculitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Foot Callus			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Itchy Rash			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Night Sweats			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Seborrhoeic Dermatitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin Rash			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Tinea Corporis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Urethral Irritation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Achilles Tendonitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Back Pain			

subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Low Back Pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Muscle Swelling			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Musculoskeletal Pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pain In Arm			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Infections and infestations			
Acute Hepatitis A			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Acute Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cold			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Cold Sore			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Common Cold			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Coryzal Illness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Coryzal Symptoms			

subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	2
Eye Infection		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	0
Flu Symptoms		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Folliculitis		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	0
Fungal Infection		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Furuncle		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	0
Gingivitis		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Gonorrhoea		
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)
occurrences (all)	2	3
Helicobacter Pylori Infection		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	0
Influenza B Virus Infection		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	1	0
Lymphogranuloma Venereum		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Pharyngeal Gonococcal Infection		

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Proctitis Herpes			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ringworm Of Body			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Salmonella Gastroenteritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Shingles			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Syphilis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Tonsillitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Tooth Abscess			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Glucose Tolerance Impaired			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vitamin D Deficiency			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2015	<p>Schedule amended to allow for repeat testing of a participant's viral load, until this falls below the level of detectability. Trial assessment schedule has been split into two stages, pre and post randomisation, with randomisation becoming a separate visit to ensure all participants have a common baseline. All visits after randomisation are now referred to as post randomisation weeks (PR week), which has been updated throughout.</p> <p>Eligibility assessments including routine blood results and resting 12-lead ECG need to be within 14 days of randomisation.</p> <p>Wording clarified for enrolment exclusion criteria 22.</p> <p>Removed the requirement for participants to attend visits fasted.</p> <p>Changes to the trial assessment schedule only: 1) Screening/baseline visit is now referred to as screening only. 2) Follow up visit at week 08 has been removed. 3) For several visits the volumes and timings of blood samples have been changed. Total blood volume taken across the protocol has increased by 17ml. 4) Visits where quality of life questionnaires are required have changed.</p> <p>Further clarification on the vaccination visits has been included: 1) Specified that the first vaccination (Chad) at PR week 00 must take place within 1 week of randomisation. For participants in Arm A, this visit can be completed over the phone. 2) There is a window of 7 days between the two vaccinations given at PR week 00 and PR08 Day 1. 3) Preliminary results from the BCN01 study are now available. 4) Results from the START study are now available</p>
03 June 2015	<p>Continued:</p> <p>Event reporting section has been updated : 1) Only grade 3 adverse events are reportable prior to randomisation. Grade 4 events are reportable throughout the study as SAEs. 2) Pregnancy in a partner is now considered a notable event. 3) Vaccine related events have been added to the notable events and are listed in Appendix IV. 4) For SAEs, participants must be identified by study number, 3 letter code and year of birth only. 5) Clarification that HERVs may be investigated as an exploratory outcome. 6) Re-clarification of the end of the interventional phase of the study and end of study.</p>
23 July 2015	<p>Re-clarification of the investigator's event reporting responsibilities.</p>
18 May 2016	<p>Additional QTc information. Change of QTc and bradycardia eligibility criteria. Trial Assessment Schedule only: Additional ECGs at PR10-1 and PR16 included</p> <p>Eligibility has been updated to: 1) Enable sites to use either Hepatitis C RNA or Hepatitis C antigen test to exclude current infection. 2) Enforce use of the CKD-EPI equation to calculate eGFR.</p> <p>Clarification on use of ART prior to enrolment</p> <p>Removed requirement for participants to return empty/part used Raltegravir</p> <p>Removal co-enrolment in UK Register of HIV seroconverters.</p>

20 October 2016	<p>Addition of Cohort II – Previously diagnosed participants</p> <p>Additional 18ml blood sample for Merck assay at PR11-1.</p> <p>Change of eGFR eligibility criteria .</p> <p>References to TMG updated to PMG.</p>
15 October 2019	<p>Change to coordinating centre address and Clinical Project Manager.</p> <p>Addition of annual follow up phase to visit tables.</p> <p>Added lost to follow up definition during long-term follow-up.</p> <p>Change of long-term follow-up requirements.</p> <p>Added clarification on the notification requirements for Notable Events during long-term follow-up.</p>
14 June 2022	<p>Added VIRIAS substudy information including background, rationale, number of participants, eligibility criteria and visit procedures.</p> <p>Addition of VIRIAS substudy references.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32085823>