

**Clinical trial results:**

A phase IIa randomized, placebo controlled, double blinded study to evaluate the safety and immunogenicity of iHIVARNA-01 in chronically HIV-infected patients under stable combined antiretroviral therapy.

Summary

EudraCT number	2016-002724-83
Trial protocol	BE ES NL
Global end of trial date	27 November 2018

Results information

Result version number	v2 (current)
This version publication date	02 August 2019
First version publication date	14 June 2019
Version creation reason	<ul style="list-style-type: none">• Correction of full data set On request of the AEMPS, the following warning has been added to the description arm of the relevant treatment groups: "see limitations and caveats section"
Summary attachment (see zip file)	SAR (20181127_SAR_ihivarna_V1.0 signed.doc)

Trial information**Trial identification**

Sponsor protocol code	iHIVARNA-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02888756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IDIBAPS
Sponsor organisation address	Villaroell, Barcelona, Spain,
Public contact	Hospital Clínic, IDIBAPS, 34 9322754002884, fgarcia@clinic.cat
Scientific contact	Hospital Clínic, IDIBAPS, 34 9322754002884, fgarcia@clinic.cat
Sponsor organisation name	Erasmus MC
Sponsor organisation address	Wytemaweg 80, Rotterdam, Netherlands, 3015 GE
Public contact	Dr R Gruters, Erasmus MC, 31 107032100, r.gruters@erasmusmc.nl
Scientific contact	Dr R Gruters, Erasmus MC, 31 107032100, r.gruters@erasmusmc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	27 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2018
Global end of trial reached?	Yes
Global end of trial date	27 November 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- safety and tolerability, as measured by the total number of adverse events.
- immunogenicity of an immunization schedule with HIV-TriMix-mRNA as measured by the increase in frequency of the HIV-specific T-cell responses between baseline and 2 weeks after the last injection as compared to both control groups, immunized with TriMix-mRNA only or WFI only

Protection of trial subjects:

In every visit subjects were attended by the study team (at least a physician and a nurse), during this visits all vitals were checked and information about any side effect collected. This team accompanied the subject during all procedures (blood extraction, product administration..) and made everything possible to minimize distress. In case of a painful procedure a painkiller could have been prescribed. Subject had a direct telephone line to contact the study team in any case they considered this necessary.

Background therapy:

cART therapy for chronic HIV-1 infection, before and during immunization. Two weeks after the last immunization cART was interrupted. cART was restarted at week 12 after interruption or earlier at the doctor's decision.

Evidence for comparator:

Not applicable

Actual start date of recruitment	27 March 2017
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	Belgium: 12
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 19
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	33
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period started March 27, 2017 and ended June 19, 2017 in Spain. The recruitment period in Belgium was April 3, 2017 until June 30, 2017. In The Netherlands two patients were screened on May 29 and June 14, 2017.

Pre-assignment

Screening details:

patients were eligible for enrollment in case of a stably treated HIV-1 infection, as determined by a viral load ≤ 50 copies/mL, a current CD4+ cell count ≥ 450 cells/ μ L and a nadir CD4+ cell count of ≥ 350 cells/ μ L. No chronic co-infections with hepatitis B and/or C virus were allowed.

Pre-assignment period milestones

Number of subjects started	38 ^[1]
Number of subjects completed	33

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 3
Reason: Number of subjects	Consent withdrawn by subject: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Five subjects that were screened, were not included in the trial due to the decision of the physician (n=3) or withdrawn consent (n=2).

Period 1

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

Blinding implementation details:

A randomization code list was generated by an independent statistician prior to start of the study (using R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The label containing the randomization code was attached to the appropriate IMP at the central production facility in order to keep the blind for both the sponsor and investigators.

Arms

Are arms mutually exclusive?	Yes
Arm title	HTI/TriMix

Arm description:

HTI HIVACAT immunogen with TriMix adjuvans both in form of mRNA.

See limitations and caveats section

Arm type	Experimental
Investigational medicinal product name	iHIVARNA-01
Investigational medicinal product code	
Other name	HTI/TriMix, HIVACAT/TriMix
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

300 microgram TriMix and 900 microgram HIVACAT. Echo-guided intranodal injection in lymph nodes of the groin.

Arm title	TriMix
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Arm description:	
TriMix adjuvans alone. TriMix mRNA encodes for CD40L, caTLR4 and CD70	
Arm type	adjuvans alone
Investigational medicinal product name	TriMix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

300 microgram TriMix. Echo-guided intranodal injection in lymph nodes of the groin.

Arm title	Water for Injection WFI
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Arm description:

Water for injection

Arm type	Placebo
Investigational medicinal product name	WFI
Investigational medicinal product code	
Other name	water for injection
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Intranodal injection of placebo, water for injection.

Number of subjects in period 1	HTI/TriMix	TriMix	Water for Injection WFI
Started	16	9	8
Completed	16	9	8

Period 2	
Period 2 title	Analytical treatment interruption
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer
Blinding implementation details:	
See vaccination period	
Arms	
Are arms mutually exclusive?	Yes

Arm title	HTI/TriMix
Arm description: HTI HIVACAT immunogen with TriMix adjuvans both in form of mRNA See limitations and caveats section	
Arm type	Experimental
Investigational medicinal product name	iHIVARNA-01
Investigational medicinal product code	
Other name	HTI/TriMix, HIVACAT/TriMix
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intralymphatic use
Dosage and administration details: 300 microgram TriMix and 900 microgram HIVACAT. Echo-guided intranodal injection in lymph nodes of the groin.	
Arm title	TriMix
Arm description: TriMix adjuvans alone. TriMix mRNA encodes for	
Arm type	adjuvans alone
Investigational medicinal product name	TriMix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intralymphatic use
Dosage and administration details: 300 microgram TriMix mRNA	
Arm title	Water for Injection WFI
Arm description: Water for injection	
Arm type	Placebo
Investigational medicinal product name	WFI
Investigational medicinal product code	
Other name	water for injection
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use
Dosage and administration details: Intranodal injection of placebo, water for injection.	

Number of subjects in period 2^[2]	HTI/TriMix	TriMix	Water for Injection WFI
Started	15	9	8
Completed	5	3	3
Not completed	10	6	5
Physician decision	10	6	5

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One subject experienced an SAE and it was decided that the subject should not stop cART.

Baseline characteristics

Reporting groups

Reporting group title	HTI/TriMix
Reporting group description: HTI HIVACAT immunogen with TriMix adjuvans both in form of mRNA. See limitations and caveats section	
Reporting group title	TriMix
Reporting group description: TriMix adjuvans alone. TriMix mRNA encodes for CD40L, caTLR4 and CD70	
Reporting group title	Water for Injection WFI
Reporting group description: Water for injection	

Reporting group values	HTI/TriMix	TriMix	Water for Injection WFI
Number of subjects	16	9	8
Age categorical Units: Subjects			
Adults (18-64 years)	16	9	8
Age continuous			
Age reported by group			
Units: years			
median	44.5	46.0	40
inter-quartile range (Q1-Q3)	36.0 to 54.0	37.0 to 51.0	35.0 to 54.0
Gender categorical Units: Subjects			
Female	1	0	0
Male	15	9	8
Mode of HIV transmission reported per group Units: Subjects			
men having sex with men	14	8	7
heterosexual	1	0	1
Intravenous Drug Abuse	0	1	0
Unknown	1	0	0
Median CD4+ T cell count at baseline Units: cells/microlitre			
median	793	708	742
inter-quartile range (Q1-Q3)	689 to 1041	592 to 961	679 to 918

Reporting group values	Total		
Number of subjects	33		
Age categorical Units: Subjects			
Adults (18-64 years)	33		
Age continuous			
Age reported by group			
Units: years			
median			

inter-quartile range (Q1-Q3)	-		
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Gender categorical Units: Subjects			
Female	1		
Male	32		
Mode of HIV transmission reported per roup Units: Subjects			
men having sex with men	29		
heterosexual	2		
Intravenous Drug Abuse	1		
Unknown	1		
Median CD4+ T cell count at baseline Units: cells/microlitre median inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	HTI/TriMix
Reporting group description: HTI HIVACAT immunogen with TriMix adjuvans both in form of mRNA. See limitations and caveats section	
Reporting group title	TriMix
Reporting group description: TriMix adjuvans alone. TriMix mRNA encodes for CD40L, caTLR4 and CD70	
Reporting group title	Water for Injection WFI
Reporting group description: Water for injection	
Reporting group title	HTI/TriMix
Reporting group description: HTI HIVACAT immunogen with TriMix adjuvans both in form of mRNA See limitations and caveats section	
Reporting group title	TriMix
Reporting group description: TriMix adjuvans alone. TriMix mRNA encodes for	
Reporting group title	Water for Injection WFI
Reporting group description: Water for injection	

Primary: Safety

End point title	Safety
End point description: grade 3 or above adverse events during the entire study period	
End point type	Primary
End point timeframe: Entire study period 30 weeks	

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	9	8	
Units: Adverse Events				
Adverse Events	2	0	1	

Statistical analyses

Statistical analysis title	Safety
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.38
Method	Cochran-Mantel-Haenszel

Primary: Immunogenicity

End point title	Immunogenicity
End point description:	
Difference in log10 mean Elispsot results between groups, with WFI as reference	
End point type	Primary
End point timeframe:	
Log10(week6 Elispot)-log10(baseline Elispot), Log10(week10 Elispot)-log10(baseline Elispot), Log10(week18 Elispot)-log10(baseline Elispot)	

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16 ^[1]	9 ^[2]	8	
Units: Spot Forming Units				
log mean (confidence interval 95%)				
week 6	-0.07 (-0.35 to 0.20)	0.18 (-0.17 to 0.52)	0.01 (-0.57 to 0.60)	
week 10	0.16 (-0.42 to 0.75)	0.26 (-0.52 to 1.05)	0.04 (-0.86 to 0.94)	
week 18	-0.08 (-0.57 to 0.42)	-0.12 (-0.61 to 0.36)	0.45 (-0.52 to 1.42)	

Notes:

[1] - multiple imputation for week 10 and week 18

[2] - multiple imputation for week 10 and week 18

Statistical analyses

Statistical analysis title	linear mixed effects regression
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.14 ^[4]
Method	Mixed models analysis

Notes:

[3] - multiple imputation for later time points

[4] - week 6

Statistical analysis title	linear mixed effects regression
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3 ^[5]
Method	Mixed models analysis

Notes:

[5] - week 10

Statistical analysis title	mixed linear effects regression
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 ^[6]
Method	Mixed models analysis

Notes:

[6] - week 18

Secondary: T cell responses W6, W30

End point title	T cell responses W6, W30
End point description:	
Difference between vaccination arms in HIV-specific T cell responses, with WFI as reference	
End point type	Secondary
End point timeframe:	
Log10(W6 Elispot), log10 (W30 Elispot)	

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	7	6 ^[7]	
Units: Spot Forming Units				
log mean (confidence interval 95%)				
week 6	0.01 (-0.56 to 0.57)	0.17 (-0.47 to 0.81)	2.65 (1.94 to 3.37)	
week 30	0.03 (-0.54 to 0.49)	0.12 (-0.48 to 0.71)	3.19 (2.64 to 3.73)	

Notes:

[7] - for week 30 there were 8 subjects available for analysis

Statistical analyses

Statistical analysis title	linear mixed effects regression
Statistical analysis description:	
linear mixed effects regression with fixed effect for intervention group and random intercept by site.	
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [8]
Method	Mixed models analysis

Notes:

[8] - week 6

Statistical analysis title	linear mixed effects regression
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [9]
Method	Mixed models analysis

Notes:

[9] - week 30

Secondary: Time to viral rebound

End point title	Time to viral rebound
End point description:	median time to viral rebound (days)
End point type	Secondary
End point timeframe:	
Analytical Treatment Interruption period:	week 6 week 30

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15 ^[10]	9	8	
Units: time (days)				
median (confidence interval 95%)	50 (33 to 57)	55.5 (43 to 77)	58 (36 to 72)	

Notes:

[10] - One participant did not stop cART, due to unrelated SAE

Statistical analyses

Statistical analysis title	frailty model
Statistical analysis description:	A shared frailty model was fitted with intervention group as independent variable and frailties for site to compare time from W6 until viral rebound between the three intervention groups; the cause-specific hazard ratio with 95% confidence interval was estimated where events such as restart of cART and death were handled as competing risks.
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Regression, Cox

Secondary: Reduction in plasma viral load

End point title	Reduction in plasma viral load
End point description:	difference in log10 copies/ml pvl, compared to placebo WFI
End point type	Secondary
End point timeframe:	week 6- restart of cART

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	9	8	
Units: copies/ml				
log mean (confidence interval 95%)	-0.17 (-1.10 to 0.77)	-0.14 (-1.18 to 0.90)	1.26 (0.21 to 2.31)	

Statistical analyses

Statistical analysis title	linear mixed effects model
Statistical analysis description:	This model includes (nested) random intercepts for subject and site and fixed effects for randomization group, time (days since W6) and the interaction term between time and randomization group
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Mixed models analysis

Secondary: Functional cure at week 18

End point title	Functional cure at week 18
End point description:	Number of participants with suppression of HIV to undetectable levels, at the end of the cART interruption period (week 18. This could be explained as functional cure.
End point type	Secondary

End point timeframe:
week 18

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	7	8	
Units: participants with pvl <50 copies/ml	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Primary immune response.

End point title	Primary immune response.
End point description: Number of participants with an increase in frequency of at least 0.7 log10 HIV-specific T-cell responses between baseline and week 6, two weeks after the last vaccination.	
End point type	Secondary
End point timeframe: week 6	

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	7	5	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: CD8 T cell-mediated virus suppression

End point title	CD8 T cell-mediated virus suppression
End point description: Mean change in CD8+ T-cell HIV suppressive capacity measured after in vitro re-stimulation: (log10 virus CD4-(log10 virus CD4CD8). Suppressive capacity is measured in the decrease in HIV p24 production in the supernatant. Value for WFI is mean change from baseline. other arms are mean difference from WFI.	
End point type	Secondary
End point timeframe: week 4 compared to baseline	

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	5	
Units: copies/ml				
log mean (confidence interval 95%)				
Ex vivo (2:1)	-0.10 (-0.78 to 0.57)	-0.60 (-1.36 to 0.16)	0.07 (-0.50 to 0.63)	
Ex vivo (0.1:1)	0.17 (-0.37 to 0.72)	-0.09 (-0.70 to 0.51)	-0.05 (-0.51 to 0.40)	
Stimulated (2:1)	0.15 (-0.69 to 0.99)	0.22 (-0.73 to 1.16)	0.18 (-0.48 to 0.85)	
Stimulated (0.1:1)	-0.65 (-1.26 to -0.05)	-1.32 (-2.00 to -0.65)	0.41 (-0.08 to 0.90)	

Statistical analyses

Statistical analysis title	mixed effects linear regression
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Statistical analysis description:

This model included (nested) random intercepts for subject and site and fixed effects for time and the interaction term between time and randomization group.

Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.21
Method	Mixed models analysis

Notes:

[11] - Ex vivo 2:1

Statistical analysis title	mixed effects linear regression
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Statistical analysis description:

This model included (nested) random intercepts for subject and site and fixed effects for time and the interaction term between time and randomization group.

Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.55
Method	Mixed models analysis

Notes:

[12] - Ex vivo 0.1:1

Statistical analysis title	mixed effects linear regression
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Statistical analysis description:

This model included (nested) random intercepts for subject and site and fixed effects for time and the interaction term between time and randomization group.

Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.89
Method	Mixed models analysis

Notes:

[13] - Stimulated 2:1

Statistical analysis title	mixed effects linear re...
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Statistical analysis description:

This model included (nested) random intercepts for subject and site and fixed effects for time and the interaction term between time and randomization group.

Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.002
Method	Mixed models analysis

Notes:

[14] - Stimulated 0.1:1

Secondary: Effect on reservoir as measured by cell associated RNA

End point title	Effect on reservoir as measured by cell associated RNA
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End point description:

change per day in log 10 RNA copies/ million CD4 T cells

End point type	Secondary
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End point timeframe:

0-30 days, 30-80 daays, 80-150 days, >150 days

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	9	8	
Units: Log RNA copies				
log mean (confidence interval 95%)				
0-30 days	-0.001 (-0.009 to 0.007)	-0.002 (-0.012 to 0.008)	-0.004 (-0.011 to 0.003)	
30-80 days	-0.006 (-0.015 to 0.003)	-0.001 (-0.013 to 0.010)	0.032 (0.024 to 0.040)	
80-150 days	0.002 (-0.008 to 0.012)	0.003 (-0.008 to 0.015)	-0.016 (-0.024 to -0.008)	
>150 days	0.002 (-0.008 to 0.011)	-0.001 (-0.012 to 0.010)	-0.004 (-0.011 to 0.003)	

Statistical analyses

Statistical analysis title	mixed effects linear regression
Statistical analysis description: This model includes (nested) random intercepts for subject and site and fixed effects for time (days since W0) and the interaction term between time and randomization group	
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.69
Method	Mixed models analysis

Notes:

[15] - a piecewise linear model was fitted with breakpoints chosen based on lowess graphs

Secondary: Effect on reservoir as measured by proviral DNA

End point title	Effect on reservoir as measured by proviral DNA
End point description: Change per day in log10 HIV proviral cp/million CD4+ T cells	
End point type	Secondary
End point timeframe: Time periods were based on the breakpoints of a piecewise linear model, Figure 5 in SAR	

End point values	HTI/TriMix	TriMix	Water for Injection WFI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	9	8	
Units: log10 copies/million CD4 T cells				
log mean (confidence interval 95%)				
0-90 days	-0.002 (-0.007 to 0.003)	-0.001 (-0.007 to 0.004)	0.007 (0.003 to 0.011)	
90-130 days	0.004 (-0.010 to 0.019)	0.004 (-0.013 to 0.020)	-0.003 (-0.015 to 0.008)	
>130 days	-0.001 (-0.007 to 0.005)	-0.002 (-0.010 to 0.006)	-0.003 (-0.007 to 0.002)	

Statistical analyses

Statistical analysis title	mixed effects linear regression
Statistical analysis description: This model includes (nested) random intercepts for subject and site and fixed effects for time (days since W0) and the interaction term between time and randomization group	
Comparison groups	HTI/TriMix v TriMix v Water for Injection WFI

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	= 0.99
Method	Mixed models analysis

Notes:

[16] - a piecewise linear model was fitted with breakpoints chosen based on lowess graphs

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire study period 30 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	HTI/TriMix
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Reporting group description:

HTI HIVACAT immunogen with TriMix adjuvans both in form of mRNA

Reporting group title	TriMix
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Reporting group description:

TriMix adjuvans alone. TriMix mRNA encodes for

Reporting group title	Water for Injection WFI
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Reporting group description:

Water for injection

Serious adverse events	HTI/TriMix	TriMix	Water for Injection WFI
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	0 / 9 (0.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	HTI/TriMix	TriMix	Water for Injection WFI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	9 / 9 (100.00%)	8 / 8 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Chills			
subjects affected / exposed	2 / 16 (12.50%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	2	2	2
Cyst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	2 / 16 (12.50%)	3 / 9 (33.33%)	2 / 8 (25.00%)
occurrences (all)	3	5	4
Influenza like illness			
subjects affected / exposed	1 / 16 (6.25%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Infusion site extravasation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	2
Injection site pain			
subjects affected / exposed	3 / 16 (18.75%)	2 / 9 (22.22%)	2 / 8 (25.00%)
occurrences (all)	3	3	4
Injection site pruritus			

subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
Injection site reaction			
subjects affected / exposed	1 / 16 (6.25%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Malaise			
subjects affected / exposed	3 / 16 (18.75%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	6	1	2
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Tenderness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Urethritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Erectile dysfunction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Dysphonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Productive cough			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Burnout syndrome			
subjects affected / exposed	0 / 16 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Mental disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Aphasia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	6 / 16 (37.50%)	1 / 9 (11.11%)	4 / 8 (50.00%)
occurrences (all)	7	1	8
Hypoaesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Muscle contractions involuntary			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Eye disorders			

Vitreous floaters subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Gastrointestinal disorders			
Anal fissure subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	4 / 9 (44.44%) 4	2 / 8 (25.00%) 2
Dry mouth subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 9 (11.11%) 1	1 / 8 (12.50%) 1
Dysphagia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Enterocolitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1
Food poisoning subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 9 (0.00%) 0	2 / 8 (25.00%) 3
Oesophageal pain subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1
Oral dysaesthesia			

subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Night sweats			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 16 (6.25%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Rash macular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Back pain			

subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Groin pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	5 / 16 (31.25%)	1 / 9 (11.11%)	2 / 8 (25.00%)
occurrences (all)	6	1	5
Neck pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eyelid infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Gingivitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hepatitis viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Laryngitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Sexually transmitted disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 16 (25.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	5	0	1
Metabolism and nutrition disorders			
Gout			

subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2017	Temporary hold of recruitment for interim analysis. As a result of poor immunogenicity results from the phase I trial. After analysis the study was stopped for reasons of futility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 November 2017	After interim analysis the trial was stopped for futility as the specified difference of 0.7 log ₁₀ mean Elispot increase in the vaccine group compared with placebo, was not observed.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limited number of subjects for statistical analysis due to early termination.
An error in the vaccine was discovered after the trial. An extra startcodon 5' of the HIVACAT startcodon is likely to greatly impair its expression and immunogenicity.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30289805>