Clinical trial results:
Early administration of anti-latency reversing therapy and broadly neutralizing antibodies to limit the establishment of the HIV-1 reservoir during initiation of antiretroviral treatment - a randomized controlled trial (eCLEAR)

Summary

EudraCT number	2015-002234-53
Trial protocol	DK GB
Global end of trial date	17 July 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	eCLEAR-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03041012
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Infectious Diseases, Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Ole Schmeltz Søgaard, Department of Infectious Diseases, Aarhus University Hospital, 0045 78452842, olesoega@rm.dk
Scientific contact	Ole Schmeltz Søgaard, Department of Infectious Diseases, Aarhus University Hospital, 0045 78452842, olesoega@rm.dk

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	01 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2020
Global end of trial reached?	Yes
Global end of trial date	17 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of early viral reactivation by latency reversing agents (LRA) and/or administration of potent broadly neutralizing antibodies (bNAbs) on the size of the latent HIV-1 reservoir in treatment naïve HIV-1 patients initiating ART

Protection of trial subjects:

There is now considerable experience with the human safety profile of romidepsin. As of 31 December 2011, more than 1300 patients have been treated with romidepsin in clinical studies, and of those a total of 891 patients with at least one dose of romidepsin as monotherapy. The experience with 3BNC177 is sparse, but both uninfected and HIV-1infected individuals were given a single dose IV and monitored for 56 days. A total of 37 individuals have received 3BNC117 at doses ranging from 1 to 30 mg/kg, and there have been no significant AE related to 3BNC117 to date. Romidepsin is better characterized than 3BNC117, but both IMPs require monitoring and safety monitoring is described below:

Safety will be monitored by vital signs, clinical laboratory tests, history and physical examinations if needed and the rate and severity of AE. If indicated in the opinion of the investigator, a physical examination will be performed prior to and after completed infusion. Routine biochemistry (safety) will be performed prior to infusion. Infusion is postponed in case of unacceptable laboratory values prior to infusion, and laboratory tests may be repeated, as clinically indicated, to obtain acceptable values before withdraw from the study:
o Hepatic transaminases (AST or ALT) ≥3 x upper limit of normal (ULN)
o Serum total bilirubin ≥3 ULN
o Estimated glomerular filtration rate (eGFR) ≤60 mL/min (based on serum creatinine or other appropriate validated markers)
o Platelet count ≤100 x10^9/L
o Absolute neutrophil count ≤1x10^9/L
o Serum potassium, magnesium, phosphorus outside ≥1.5 ULN/LLN
o Total calcium (corrected for serum albumin) or ionized calcium ≥1.5 ULN/LLN

A baseline ECG will be obtained at screening.
Upon completion of follow-up specified in this protocol at day 365, study subjects who do not enter the ATI will resume routine treatment and control following standard treatment guidelines.

Background therapy:

All four arms were started on integrase-inhibitor-based triple-ART regimen.

Evidence for comparator: -

Actual start date of recruitment	16 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Denmark: 47
Worldwide total number of subjects	59
EEA total number of subjects	47

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)	57
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible individuals were given written information upon diagnosed with HIV-1 to participate in the study unless the individual refuses.
Eligible individuals were recruited from 16 January 2017 to 3 March 2020.

Pre-assignment

Screening details:

Screening occurred within 4 weeks before the baseline visit at day 0.

Newly diagnosed ART-naive participants aged 18 with a confirmed HIV-1 diagnosis and a CD4+ T cell count of >200 cells per mm3 at screening were recruited by study physicians.

During screening, we excluded 25% of the newly diagnosed individuals due to low CD4+ T cell count.

Period 1

Period 1 title	Main
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ART alone
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	ART+3BNC117
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	3BNC117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 30 mg/kg	
Arm title	ART+romidepsin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	romidepsin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5mg per m2	
Arm title	ART+3BNC117+romidepsin
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	3BNC117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
30 mg/kg

Investigational medicinal product name	romidepsin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
5mg per m2

Number of subjects in period 1	ART alone	ART+3BNC117	ART+romidepsin
Started	15	15	13
Completed	15	13	10
Not completed	0	2	3
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	1	2

Number of subjects in period 1	ART+3BNC117+romidepsin
Started	16
Completed	14
Not completed	2
Consent withdrawn by subject	2
Adverse event, non-fatal	-
Lost to follow-up	-

Period 2

Period 2 title	ATI
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	ART alone
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	ART+3BNC117
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	3BNC117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 30 mg/kg	
Arm title	ART+romidepsin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	romidepsin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5mg per m2	
Arm title	ART+3BNC117+romidepsin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	3BNC117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 30 mg/kg	
Investigational medicinal product name	romidepsin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5mg per m2	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Yes, period 1 is baseline.

Number of subjects in period 2[2][3]	ART alone	ART+3BNC117	ART+romidepsin
Started	4	5	5
ATI	4	5	5
Completed	4	5	5

Number of subjects in period 2[2][3]	ART+3BNC117+romidepsin
Started	6
ATI	6
Completed	6

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: ATI was optional.

[3] - 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: ATI was optional.

Baseline characteristics

Reporting groups	
Reporting group title	ATI

Reporting group description: -

Reporting group values	ATI	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	37		
full range (min-max)	29 to 46	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	18	18	

End points

End points reporting groups	
Reporting group title	ART alone
Reporting group description: -	
Reporting group title	ART+3BNC117
Reporting group description: -	
Reporting group title	ART+romidepsin
Reporting group description: -	
Reporting group title	ART+3BNC117+romidepsin
Reporting group description: -	
Reporting group title	ART alone
Reporting group description: -	
Reporting group title	ART+3BNC117
Reporting group description: -	
Reporting group title	ART+romidepsin
Reporting group description: -	
Reporting group title	ART+3BNC117+romidepsin
Reporting group description: -	

Primary: HIV-1 reservoir	
End point title	HIV-1 reservoir
End point description: Median decline	
End point type	Primary
End point timeframe: Day 0-365	

End point values	ART alone	ART+3BNC117	ART+romidepsin	ART+3BNC117+romidepsin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	10	14
Units: intact proviruses710^6 CD4+ T cells				
median (inter-quartile range (Q1-Q3))	2709 (734 to 11442)	5032 (2013 to 26165)	5382 (2583 to 8695)	10274 (355 to 18846)

Statistical analyses

Statistical analysis title	Size of HIV-1 reservoir
Comparison groups	ART+3BNC117+romidepsin v ART alone

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Size of HIV-1 reservoir
Comparison groups	ART alone v ART+3BNC117
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Size of HIV-1 reservoir
Comparison groups	ART+romidepsin v ART alone
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.53
Method	Wilcoxon (Mann-Whitney)

Primary: ATI	
End point title	ATI
End point description: ART-free virological control	
End point type	Primary
End point timeframe: Day 400	

End point values	ART alone	ART+3BNC117	ART+romidepsin	ART+3BNC117 +romidepsin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	5	6
Units: %	2	1	1	3

Statistical analyses

Statistical analysis title	ATI
Comparison groups	ART alone v ART+3BNC117+romidepsin v ART+3BNC117 v ART+romidepsin
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.025 [1]
Method	Log-rank test

Notes:

[1] - We compared 3BNC117-sensitive individuals to all other ATI participants, but the difference in virologic control between the groups remained significant (P=0.025)

Secondary: FISH flow

End point title	FISH flow

End point description:

End point type	Secondary

End point timeframe:

Day 0-30

End point values	ART+3BNC117	ART+romidepsin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: p24+ cells per 10^6 CD4+ T cells				
median (inter-quartile range (Q1-Q3))	167 (62 to 359)	80 (20 to 132)		

Statistical analyses

No statistical analyses for this end point

Secondary: HIV-1 specific immunity

End point title	HIV-1 specific immunity

End point description:

End point type	Secondary

End point timeframe:

Day 0-365

End point values	ART alone	ART+3BNC117 +romidepsin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: %				
median (inter-quartile range (Q1-Q3))	0.31 (0.07 to 0.57)	0.95 (0.52 to 1.74)		

Statistical analyses

Statistical analysis title	HIV-1 immunity
Comparison groups	ART alone v ART+3BNC117+romidepsin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Post-hoc: 3BNC117 sensitivity

End point title	3BNC117 sensitivity[2]

End point description:

End point type	Post-hoc

End point timeframe:

End of study

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only done for individuals given 3BNC117.

End point values	ART+3BNC117	ART+3BNC117 +romidepsin	ART+3BNC117	ART+3BNC117 +romidepsin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	5	6
Units: 18	8	10	2	3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Start to end of study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03
Reporting groups	
Reporting group title	ART alone
Reporting group description: -	
Reporting group title	ART+3BNC117+romidepsin
Reporting group description: -	

Serious adverse events	ART alone	ART+3BNC117+romidepsin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	2 / 16 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Radiculitis brachial			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
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: 5 %

Non-serious adverse events	ART alone	ART+3BNC117+romidepsin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	15 / 16 (93.75%)	
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 15 (20.00%)	4 / 16 (25.00%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Fatigue			
subjects affected / exposed	2 / 15 (13.33%)	5 / 16 (31.25%)	
occurrences (all)	4	5	
Infections and infestations			
Sexually transmitted disease			
subjects affected / exposed	6 / 15 (40.00%)	5 / 16 (31.25%)	
occurrences (all)	11	6	
Upper respiratory tract infection			
subjects affected / exposed	2 / 15 (13.33%)	4 / 16 (25.00%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Our study also has some limitations and may not be generalizable to all newly diagnosed individuals due to the study's stringent exclusion criteria.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3625360