



Clinical trial results:

Combining a TLR9 agonist with broadly neutralizing antibodies for reservoir reduction and immunological control of HIV infection: An investigator-initiated randomized, placebo-controlled, phase IIa trial (TITAN)

Summary

EudraCT number	2018-001165-16
Trial protocol	DK NO
Global end of trial date	09 June 2022

Results information

Result version number	v1 (current)
This version publication date	03 October 2024
First version publication date	03 October 2024
Summary attachment (see zip file)	Paper (Impact of a TLR9 agonist and bNAbs.pdf)

Trial information

Trial identification

Sponsor protocol code	TITAN-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03837756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 45, Aarhus, Denmark,
Public contact	Ole Schmeltz Sogaard, Department of Infectious Diseases, Aarhus University Hospital, 0045 78452842, olesoega@rm.dk
Scientific contact	Ole Schmeltz Sogaard, 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 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2022
Global end of trial reached?	Yes
Global end of trial date	09 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of a TLR9 agonist (Lefitolimod) and/or administration of potent bNAbs (3BNC117 and 10-1074) on time to viral rebound during analytical treatment interruption.

Protection of trial subjects:

Blood samples and participant-specific documents will not contain information that directly identifies the participant, but will be supplied with a study identification code unique for each subject. All study material will be treated in accordance with the national law and Data Protection Agency.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2018
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	Norway: 14
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	Australia: 5
Worldwide total number of subjects	46
EEA total number of subjects	41

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)	46
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Eligible study subjects will be recruited according to local norms. To direct the information for potential eligible participants, screening on inclusion and exclusion criterias can be done by nurses or doctors at local sites involved in the study.

Pre-assignment

Screening details:

Sensitivity of the viral reservoir to neutralization by 3BNC117 and 10-1074 will be tested following the screening visit (i.e. prior to enrollment and randomization).

Pre-assignment period milestones

Number of subjects started	46
Number of subjects completed	46

Period 1

Period 1 title	Inclusion and dosing
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Because the placebo is not specifically manufactured by the producers of the IMPs, it is not possible for the placebo packaging to mimic that of the IMPs. Therefore, in order to ensure the continued blinding of the administering personnel and the participant, a nurse or similarly qualified point-of-care designee will prepare the IMP(s) in a manner so that the administering personnel remains blinded to the IMP packaging.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI

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

Dosage and administration details:

3BNC117 (30mgkg⁻¹) and 10-1074 (20mgkg⁻¹) or placebo were given as sequential intravenous (i.v.) infusions the day before starting the ATI and 3weeks into the ATI.

Arm title	TLR9/placebo
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Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Lefitolimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details:	
Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI	
Arm title	Placebo/bNAb
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details:	
Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI	
Arm title	TLR9/bNAb
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lefitolimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details:	
Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI	
Investigational medicinal product name	bNAbs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
3BNC117 (30mgkg ⁻¹) and 10-1074 (20mgkg ⁻¹) or placebo were given as sequential intravenous (i.v.) infusions the day before starting the ATI and 3weeks into the ATI.	

Number of subjects in period 1	Placebo/placebo	TLR9/placebo	Placebo/bNAb
Started	11	11	12
Completed	10	10	10
Not completed	1	1	2
Consent withdrawn by subject	1	1	1
Adverse event, non-fatal	-	-	1

Number of subjects in period 1	TLR9/bNAb
Started	12
Completed	12
Not completed	0
Consent withdrawn by subject	-
Adverse event, non-fatal	-

Period 2

Period 2 title	ATI
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI

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

Dosage and administration details:

3BNC117 (30mgkg⁻¹) and 10-1074 (20mgkg⁻¹) or placebo were given as sequential intravenous (i.v.) infusions the day before starting the ATI and 3weeks into the ATI.

Arm title	TLR9/placebo
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Lefitolimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI

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

Dosage and administration details:

3BNC117 (30mgkg⁻¹) and 10-1074 (20mgkg⁻¹) or placebo were given as sequential intravenous (i.v.) infusions the day before starting the ATI and 3weeks into the ATI.

Arm title	Placebo/bNAb
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI

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

Dosage and administration details:

3BNC117 (30mgkg⁻¹) and 10-1074 (20mgkg⁻¹) or placebo were given as sequential intravenous (i.v.) infusions the day before starting the ATI and 3weeks into the ATI.

Arm title	TLR9/bNAb
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Lefitolimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Lefitolimod (120mg) or placebo was dosed subcutaneously (s.c.) once weekly for 8weeks starting 2 weeks before the ATI and ending at the beginning of week 6 of the ATI

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

Dosage and administration details:

3BNC117 (30mgkg⁻¹) and 10-1074 (20mgkg⁻¹) or placebo were given as sequential intravenous (i.v.) infusions the day before starting the ATI and 3weeks into the ATI.

Number of subjects in period 2	Placebo/placebo	TLR9/placebo	Placebo/bNAbs
Started	10	10	10
Completed	10	10	10

Number of subjects in period 2	TLR9/bNAbs
Started	12
Completed	12

Baseline characteristics

Reporting groups

Reporting group title	Inclusion and dosing
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Reporting group description: -

Reporting group values	Inclusion and dosing	Total	
Number of subjects	46	46	
Age categorical			
Median age at enrollment was 50years (interquartile range (IQR): 41–54)			
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)	46	46	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	50		
inter-quartile range (Q1-Q3)	41 to 54	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	39	39	

End points

End points reporting groups

Reporting group title	Placebo/placebo
Reporting group description: -	
Reporting group title	TLR9/placebo
Reporting group description: -	
Reporting group title	Placebo/bNAb
Reporting group description: -	
Reporting group title	TLR9/bNAb
Reporting group description: -	
Reporting group title	Placebo/placebo
Reporting group description: -	
Reporting group title	TLR9/placebo
Reporting group description: -	
Reporting group title	Placebo/bNAb
Reporting group description: -	
Reporting group title	TLR9/bNAb
Reporting group description: -	

Primary: Time to loss of virologic control after ATI

End point title	Time to loss of virologic control after ATI
End point description:	
End point type	Primary
End point timeframe:	
25-week of ATI	

End point values	Placebo/placebo	TLR9/placebo	Placebo/bNAb	TLR9/bNAb
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	12
Units: week				
median (inter-quartile range (Q1-Q3))	4.5 (3.0 to 11)	5.0 (4.0 to 6.0)	17 (11 to 25)	14 (10 to 17)

Statistical analyses

Statistical analysis title	Time to event
Comparison groups	Placebo/placebo v TLR9/placebo v Placebo/bNAb v TLR9/bNAb

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Logrank

Secondary: Safety

End point title	Safety
End point description:	
End point type	Secondary
End point timeframe:	
Entire study	

End point values	Placebo/placebo	TLR9/placebo	Placebo/bNAb	TLR9/bNAb
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	11
Units: adverse events	51	53	52	98

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire study

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	5
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Reporting groups

Reporting group title	Placebo/placebo
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Reporting group description: -

Reporting group title	TLR9/placebo
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Reporting group description: -

Reporting group title	Placebo/bNAb
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Reporting group description: -

Reporting group title	TLR9/bNAb
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Reporting group description: -

Serious adverse events	Placebo/placebo	TLR9/placebo	Placebo/bNAb
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Vasovagal reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TLR9/bNAb		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
number of deaths (all causes)	0		
number of deaths resulting from	0		

adverse events			
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Vasovagal reaction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo/placebo	TLR9/placebo	Placebo/bNAb
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	10 / 11 (90.91%)
Injury, poisoning and procedural complications			
Injection site reaction			
subjects affected / exposed	5 / 10 (50.00%)	3 / 10 (30.00%)	2 / 11 (18.18%)
occurrences (all)	5	12	4
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	3 / 11 (27.27%)
occurrences (all)	1	5	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 10 (60.00%)	4 / 10 (40.00%)	3 / 11 (27.27%)
occurrences (all)	8	5	3
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2

Non-serious adverse events	TLR9/bNAb		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		

Injury, poisoning and procedural complications Injection site reaction subjects affected / exposed occurrences (all)	8 / 12 (66.67%) 27		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all)	7 / 12 (58.33%) 8 0 / 12 (0.00%) 0		

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? Yes

Date	Interruption	Restart date
01 February 2020	Study procedures were unfortunately severely impacted by the coronavirus disease 2019 (COVID-19) pandemic, and enrollment had to be paused for longer periods in 2020 and 2021.	-

Notes:

Limitations and caveats

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

The reported results have limitations and may not be generalizable to all PWH. Specifically, our ability to predict proviral bNAbs sensitivity based on the PhenoSense assay or sequence analysis is limited. Most enrolled participants were male.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/3769693>