Clinical trial results:
Bisphosphonate Therapy with Zoledronic acid or Tenofovir Switching to Improve Low Bone Mineral Density in HIV-Infected Adults

Summary

EudraCT number	2013-003359-39
Trial protocol	ES
Global end of trial date	26 March 2018

Results information

Result version number	v1 (current)
This version publication date	29 June 2025
First version publication date	29 June 2025

Trial information

Trial identification

Sponsor protocol code	ZEST

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Australian and New Zealand Clinical Trials Registr: ACTRN12612000776808

Notes:

Sponsors

Sponsor organisation name	Fundació Clínic per a la Recerca Biomèdica
Sponsor organisation address	Villarroel, 170, Barcelona, Spain, 08036
Public contact	Dr. Joan Albert Arnaiz, CTU (Clinical Trials Department), 34 93 227 57 07, jaarnaiz@clinic.cat
Scientific contact	Dr. Esteban Martínez, Fundació Clínic per a la Recerca Biomèdica, 34 93 227 57 07, estebanm@clinic.cat

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	22 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2017
Global end of trial reached?	Yes
Global end of trial date	26 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of zoledronic acid 5 mg IV yearly to switching from tenofovir to another antiretroviral drug on lumbar spine BMD (primary endpoint) over 2 years.

Protection of trial subjects:

Participants were protected through ethics approval, informed consent, strict eligibility criteria, regular safety monitoring, and oversight by an independent Data Safety Monitoring Board.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 July 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 57
Country: Number of subjects enrolled	Spain: 28
Worldwide total number of subjects	85
EEA total number of subjects	28

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)	85
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Number of subjects assessed for eligibility: 112
Number of subjects excluded prior to assignment: 25 (Reason: Did not meet inclusion/exclusion criteria – 22 subjects, Reason: Declined to participate – 3 subjects).
Number of subjects assigned to trial groups: 87

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF Switch

Arm description:

Participants discontinued tenofovir disoproxil fumarate (TDF) and switched to another antiretroviral drug (most commonly abacavir or raltegravir), without receiving zoledronic acid. All participants also received calcium and vitamin D supplementation as needed.

Arm type	Active comparator
Investigational medicinal product name	Tenofovir disoproxil fumarate (TDF) switch strategy
Investigational medicinal product code	
Other name	TDF switch, antirretroviral switch, ARV switch
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will switch from tenofovir disoproxil fumarate (TDF) to another potent antiretroviral drug, selected by the study physician based on prior treatment history and tolerability.
The switch options include abacavir, raltegravir, or a boosted protease inhibitor.
The selected antiretroviral will be administered orally, at least once daily, for the duration of the study (2 years).
No bisphosphonate will be administered in this arm.

Arm title	Zoledronic acid

Arm description:

Participants received intravenous zoledronic acid 5 mg at baseline and at month 12, while continuing their tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy. All participants also received calcium and vitamin D supplementation as needed.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	Aclasta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 5 mg of zoledronic acid once a year.
Administered as a single intravenous infusion.

Number of subjects in period 1	TDF Switch	Zoledronic acid
Started	42	43
Completed	38	37
Not completed	4	6
TDF reintroduced via NG tube after injury	1	-
Ceased TDF	-	3
Adverse event, non-fatal	3	-
Lost to follow-up	-	3

Baseline characteristics

Reporting groups	
Reporting group title	TDF Switch
Reporting group description:	
Participants discontinued tenofovir disoproxil fumarate (TDF) and switched to another antiretroviral drug (most commonly abacavir or raltegravir), without receiving zoledronic acid. All participants also received calcium and vitamin D supplementation as needed.	
Reporting group title	Zoledronic acid
Reporting group description:	
Participants received intravenous zoledronic acid 5 mg at baseline and at month 12, while continuing their tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy. All participants also received calcium and vitamin D supplementation as needed.	

Reporting group values	TDF Switch	Zoledronic acid	Total
Number of subjects	42	43	85
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	51	49	
standard deviation	± 12	± 11	-
Gender categorical Units: Subjects			
Male	42	40	82
Female	0	3	3
Lumbar spine BMD (L1–L4)			
Bone mineral density at the lumbar spine measured by DXA at baseline.			
Units: g/cm²			
median	1.01	0.97	
inter-quartile range (Q1-Q3)	0.88 to 1.11	0.85 to 1.10	-

End points

End points reporting groups

Reporting group title	TDF Switch
Reporting group description:	
Participants discontinued tenofovir disoproxil fumarate (TDF) and switched to another antiretroviral drug (most commonly abacavir or raltegravir), without receiving zoledronic acid. All participants also received calcium and vitamin D supplementation as needed.	
Reporting group title	Zoledronic acid
Reporting group description:	
Participants received intravenous zoledronic acid 5 mg at baseline and at month 12, while continuing their tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy. All participants also received calcium and vitamin D supplementation as needed.	

Primary: Change in lumbar spine bone mineral density (BMD)

End point title	Change in lumbar spine bone mineral density (BMD)
End point description:	
End point type	Primary
End point timeframe:	
24 months	

End point values	TDF Switch	Zoledronic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: g/cm2				
arithmetic mean (standard deviation)	2.9 (± 4.5)	7.4 (± 4.3)		

Statistical analyses

Statistical analysis title	Lumbar spine BMD change at 24 months
Comparison groups	TDF Switch v Zoledronic acid
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	6.3

Secondary: Osteoporosis

End point title	Osteoporosis
End point description: Incidence of osteoporosis (T-score <-2.5 at hip or spine)	
End point type	Secondary
End point timeframe: 24 months	

End point values	TDF Switch	Zoledronic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: Subjects	6	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signing the informed consent until 30 days after the participant's final study involvement (defined as the last dose of investigational product or the last study visit, whichever occurs later).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	TDF Switch

Reporting group description:

Participants discontinued tenofovir disoproxil fumarate (TDF) and switched to another antiretroviral drug (most commonly abacavir or raltegravir), without receiving zoledronic acid. All participants also received calcium and vitamin D supplementation as needed.

Reporting group title	Zoledronic acid

Reporting group description:

Participants received intravenous zoledronic acid 5 mg at baseline and at month 12, while continuing their tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy. All participants also received calcium and vitamin D supplementation as needed.

Serious adverse events	TDF Switch	Zoledronic acid	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 42 (14.29%)	8 / 43 (18.60%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Not related to study treatment	Additional description: The specific System Organ Class and Event Terms were not detailed in the publication. None of the SAEs were considered related to the study treatment. One death occurred in the zoledronic acid group, unrelated to treatment.		
subjects affected / exposed	6 / 42 (14.29%)	8 / 43 (18.60%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	TDF Switch	Zoledronic acid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 42 (78.57%)	37 / 43 (86.05%)	
General disorders and administration site conditions			

Not specified	Additional description: Most non-serious adverse events were not considered related to study treatment. Related events: 14 in zoledronic acid group, 22 in TDF-switch group.		
subjects affected / exposed	33 / 42 (78.57%)	37 / 43 (86.05%)	
occurrences (all)	163	114	

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.

The population was predominantly male and Caucasian, limiting generalizability. Results reflect 24-month follow-up; longer-term effects remain unknown.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29927785

http://www.ncbi.nlm.nih.gov/pubmed/31361922