Clinical trial results:
A Phase 4 Cross-Sectional Study of Bone Mineral Density in HIV-1 Infected Subjects

Summary

EudraCT number	2011-004420-35
Trial protocol	BE ES GB AT NL IT IE PT SE
Global end of trial date	06 October 2014

Results information

Result version number	v1 (current)
This version publication date	10 July 2016
First version publication date	10 July 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-104-0423

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01850212
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com

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	06 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2014
Global end of trial reached?	Yes
Global end of trial date	06 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the profile of low bone mineral density (BMD) in ≥ 50-year-old male HIV-1 infected subjects and postmenopausal female HIV-1 infected subjects taking tenofovir disoproxil fumarate (TDF)-based regimens relative to those taking non-TDF-based regimens for HIV infection.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 30
Country: Number of subjects enrolled	Portugal: 19
Country: Number of subjects enrolled	Spain: 89
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 77
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 53
Country: Number of subjects enrolled	Germany: 71
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Switzerland: 21
Worldwide total number of subjects	476
EEA total number of subjects	455

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)	385
From 65 to 84 years	91
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at study sites in Europe. The first subject was screened on 22 April 2013. The last study visit occurred on 06 October 2014.

Pre-assignment

Screening details:

516 subjects were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Male

Arm description:

Males ≥ 50 years of age on TDF or non-TDF nucleoside reverse transcriptase inhibitor (NRTI) plus ritonavir-boosted protease inhibitor (PI/r) or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.

Arm type	Experimental
Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TDF cohort: TDF as prescribed by subject's physicians.
Non-TDF cohort: non-TDF NRTI plus PI/r or non-PI/r-containing regimens.
Note that no investigational medicinal products were administered to subjects in this study. Subjects were taking their own antiretroviral medications as prescribed by their physicians.

Arm title	Female

Arm description:

Post-menopausal females on TDF or non-TDF NRTI plus PI/r or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.

Arm type	Experimental
Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TDF cohort: TDF as prescribed by subject's physicians.
Non-TDF cohort: non-TDF NRTI plus PI/r or non-PI/r-containing regimens.
Note that no investigational medicinal products were administered to subjects in this study. Subjects were taking their own antiretroviral medications as prescribed by their physicians.

Number of subjects in period 1[1]	Male	Female
Started	242	198
Completed	242	198

Notes:

[1] - 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: 15 male subjects and 21 female subjects who had a major protocol violation or missing spine or hip BMD values are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	Male
Reporting group description:	
Males ≥ 50 years of age on TDF or non-TDF nucleoside reverse transcriptase inhibitor (NRTI) plus ritonavir-boosted protease inhibitor (PI/r) or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.	
Reporting group title	Female
Reporting group description:	
Post-menopausal females on TDF or non-TDF NRTI plus PI/r or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.	

Reporting group values	Male	Female	Total
Number of subjects	242	198	440
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58	59	
standard deviation	± 6.4	± 7.3	-
Gender categorical Units: Subjects			
Female	0	198	198
Male	242	0	242
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	3	4	7
Black	18	60	78
White	220	133	353
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	12	6	18
Not Hispanic or Latino	230	192	422

End points

End points reporting groups

Reporting group title	Male

Reporting group description:

Males ≥ 50 years of age on TDF or non-TDF nucleoside reverse transcriptase inhibitor (NRTI) plus ritonavir-boosted protease inhibitor (PI/r) or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.

Reporting group title	Female

Reporting group description:

Post-menopausal females on TDF or non-TDF NRTI plus PI/r or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.

Subject analysis set title	TDF+PI/r
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects on a TDF plus PI/r-containing regimen were included in this analysis.

Subject analysis set title	TDF+Non-PI/r
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects on a TDF plus non-PI/r-containing regimen were included in this analysis.

Subject analysis set title	Non-TDF+PI/r
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects on a non-TDF NRTI plus PI/r-containing regimen were included in this analysis.

Subject analysis set title	Non-TDF+Non-PI/r
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects on a non-TDF plus non-PI/r-containing regimen were included in this analysis.

Primary: BMD Spine L1-4 T-scores in males

End point title	BMD Spine L1-4 T-scores in males[1]

End point description:

BMD T-score is the bone density compared with what is normally expected in a healthy adult of your sex. T-score is the number of units (standard deviations) that bone density is above or below the average.

End point type	Primary

End point timeframe:

Day 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	63	56	60
Units: T-score				
arithmetic mean (standard deviation)	-1.18 (± 1.775)	-0.39 (± 1.701)	-0.75 (± 1.381)	-0.6 (± 1.169)

Statistical analyses

No statistical analyses for this end point

Primary: BMD Spine L1-4 T-scores in females

End point title	BMD Spine L1-4 T-scores in females[2]

End point description:

End point type	Primary

End point timeframe:

Day 1

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	58	32	63
Units: T-score				
arithmetic mean (standard deviation)	-1.71 (± 1.303)	-1.3 (± 1.3)	-1.5 (± 1.351)	-1.09 (± 1.331)

Statistical analyses

No statistical analyses for this end point

Primary: BMD femoral neck (hip) T-scores in males

End point title	BMD femoral neck (hip) T-scores in males[3]

End point description:

End point type	Primary

End point timeframe:

Day 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	63	55	56
Units: T-score				
arithmetic mean (standard deviation)	-1.34 (± 0.799)	-1.02 (± 1.125)	-1.26 (± 0.912)	-0.9 (± 0.848)

Statistical analyses

No statistical analyses for this end point

Primary: BMD femoral neck (hip) T-scores in females

End point title	BMD femoral neck (hip) T-scores in females[4]

End point description:

End point type	Primary

End point timeframe:

Day 1

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	58	32	63
Units: T-score				
arithmetic mean (standard deviation)	-1.41 (± 1.086)	-1.17 (± 1.01)	-1.18 (± 1.191)	-1.21 (± 0.918)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with an observed T-score < -2 for spine L1-L4 in males

End point title	Percentage of subjects with an observed T-score < -2 for spine L1-L4 in males

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	63	56	60
Units: percentage of subjects				
number (not applicable)	26.2	17.5	19.6	11.7

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with an observed T-score < -2 for spine L1-L4 in females

End point title	Percentage of subjects with an observed T-score < -2 for spine L1-L4 in females

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	58	32	63
Units: percentage of subjects				
number (not applicable)	42.9	27.6	34.4	23.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with an observed T-score < -2 for femoral neck in males

End point title	Percentage of subjects with an observed T-score < -2 for femoral neck in males

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	63	55	56
Units: percentage of subjects				
number (not applicable)	18.3	19	21.8	5.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with an observed T-score < -2 for femoral neck in females

End point title	Percentage of subjects with an observed T-score < -2 for femoral neck in females

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	58	32	63
Units: percentage of subjects				
number (not applicable)	26.8	20.7	25	17.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with observed -2 ≤ T-score < -1 for spine L1-L4 in males

End point title	Percentage of subjects with observed -2 ≤ T-score < -1 for spine L1-L4 in males

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	63	56	60
Units: percentage of subjects				
number (not applicable)	39.3	23.8	30.4	23.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with observed -2 ≤ T-score < -1 for spine L1-L4 in females

End point title	Percentage of subjects with observed -2 ≤ T-score < -1 for spine L1-L4 in females

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	58	32	63
Units: percentage of subjects				
number (not applicable)	31	39.7	31.3	25.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with observed -2 ≤ T-score < -1 for femoral neck in males

End point title	Percentage of subjects with observed -2 ≤ T-score < -1 for femoral neck in males

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	63	55	56
Units: percentage of subjects				
number (not applicable)	60	25.4	41.8	39.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with observed -2 ≤ T-score < -1 for femoral neck in females

End point title	Percentage of subjects with observed -2 ≤ T-score < -1 for femoral neck in females

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	TDF+PI/r	TDF+Non-PI/r	Non-TDF+PI/r	Non-TDF+Non-PI/r
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	58	32	63
Units: percentage of subjects				
number (not applicable)	41.5	29.3	31.3	39.7

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were recorded from the signing of informed consent until the completion of all study-related procedures (single study visit)

Adverse event reporting additional description:

Safety Analysis Set

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Male

Reporting group description:

Males ≥ 50 years of age on TDF or non-TDF nucleoside reverse transcriptase inhibitor (NRTI) plus ritonavir-boosted protease inhibitor (PI/r) or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.

Reporting group title	Female

Reporting group description:

Post-menopausal females on TDF or non-TDF NRTI plus PI/r or non-PI/r-containing regimens were assessed at a single visit to collect medical history, laboratory data, and BMD information.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No subjects experienced a non-serious adverse event that occurred in at least 5% of subjects.

Serious adverse events	Male	Female	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 242 (0.41%)	0 / 198 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Meningitis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Male	Female	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 242 (0.00%)	0 / 198 (0.00%)	

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.

There were no limitations affecting the analysis or results.

Notes: