



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 \geq 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 \geq 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 | \pm 6.4 | \pm 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 \geq 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 (\pm 1.775) | -0.39 (\pm 1.701) | -0.75 (\pm 1.381) | -0.6 (\pm 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 $-2 \leq T\text{-score} < -1$ for spine L1-L4 in males

| | |
|-----------------|---|
| End point title | Percentage of subjects with observed $-2 \leq T\text{-score} < -1$ 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 $-2 \leq T\text{-score} < -1$ for spine L1-L4 in females

| | |
|-----------------|---|
| End point title | Percentage of subjects with observed $-2 \leq T\text{-score} < -1$ 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 $-2 \leq T\text{-score} < -1$ for femoral neck in males

| | |
|-----------------|--|
| End point title | Percentage of subjects with observed $-2 \leq T\text{-score} < -1$ 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 $-2 \leq T\text{-score} < -1$ for femoral neck in females

| | |
|-----------------|--|
| End point title | Percentage of subjects with observed $-2 \leq T\text{-score} < -1$ 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 \geq 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: