



Clinical trial results:

A Phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects.

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-020983-39 |
| Trial protocol | NL DE ES GB HU DK BE IT |
| Global end of trial date | 03 December 2015 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 August 2016 |
| First version publication date | 13 August 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | ING114467 |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | ViiV Healthcare |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

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 | 24 March 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 December 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the antiviral activity of GSK1349572 plus ABC/3TC FDC once daily therapy compared to Atripla over 48 weeks in HIV-1 infected therapy-naive subjects.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 February 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 27 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 10 |
| Country: Number of subjects enrolled | Romania: 18 |
| Country: Number of subjects enrolled | Spain: 235 |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | France: 27 |
| Country: Number of subjects enrolled | Germany: 71 |
| Country: Number of subjects enrolled | Italy: 31 |
| Country: Number of subjects enrolled | Australia: 18 |
| Country: Number of subjects enrolled | Canada: 59 |
| Country: Number of subjects enrolled | United States: 325 |
| Worldwide total number of subjects | 844 |
| EEA total number of subjects | 442 |

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) | 837 |
| From 65 to 84 years | 6 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Study consisted of 96 weeks double-blind phase, followed by a 48 week open-label phase.

Pre-assignment

Screening details:

A total of 844 participants (par.) were randomized (1:1) to one of the two treatment arms. Of these, 833 par. received at least one dose of study medication. Of the 11 par. who were randomized but not treated with investigational product, 7 par. withdrew consent, 3 par. were randomized in error, and 1 par. was lost to follow-up.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Double-blind phase: 96 weeks duration |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |

Arm description:

During double-blind phase, participants received a dolutegravir (DTG) 50 milligram (mg) tablet along with an Abacavir/Lamivudine (ABC/3TC) 600/300 mg tablet once daily (OD) orally, with placebo to match Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) 600/200/300 mg for 96 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dolutegravir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablet once daily for 96 weeks in double-blind randomized phase

| | |
|--|---------------------|
| Investigational medicinal product name | Abacavir/Lamivudine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600/300 mg tablet once daily for 96 weeks in double-blind randomized phase

| | |
|--|---|
| Investigational medicinal product name | Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet once daily for 96 weeks in double-blind randomized phase.

| | |
|------------------|---------------------------------------|
| Arm title | EFV/TDF/FTC 600/200/300 mg once daily |
|------------------|---------------------------------------|

Arm description:

During double-blind phase, participants received EFV/TDF/FTC 600/200/300 mg OD, with placebo to

match DTG 50 mg and ABC/3TC 600/300 mg for 96 weeks.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600/200/300 mg tablet once daily for 96 weeks in double-blind randomized phase

| | |
|--|----------------------------|
| Investigational medicinal product name | Dolutegravir (DTG) placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet once daily for 96 weeks in double-blind randomized phase

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Abacavir/Lamivudine (ABC/3TC) Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet once daily for 96 weeks in double-blind randomized phase

| Number of subjects in period 1^[1] | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily |
|---|---|--|
| Started | 414 | 419 |
| Completed | 342 | 310 |
| Not completed | 72 | 109 |
| Adverse event, serious fatal | - | 2 |
| Physician decision | 1 | 2 |
| Consent withdrawn by subject | 9 | 15 |
| Adverse event, non-fatal | 13 | 46 |
| Lost to follow-up | 17 | 18 |
| Lack of efficacy | 18 | 14 |
| Protocol deviation | 14 | 12 |

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: A total of 844 participants (par.) were randomized (1:1) to one of the two treatment arms. Of these, 833 par. received at least one dose of study medication. Of the 11 par. who were randomized but not treated with investigational product, 7 par. withdrew consent, 3 par. were randomized in error, and 1 par. was lost to follow-up.

Period 2

| | |
|------------------------------|-------------------------------------|
| Period 2 title | Open-label phase: 48 weeks duration |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |

Arm description:

Participants who completed double-blind phase continued to receive DTG 50 mg tablet along with ABC/3TC 600/300 mg tablet OD orally, for additional 48 weeks during open-label phase.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dolutegravir (DTG) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablet once daily for 48 weeks in open-label phase (96 weeks through 144 week), and during open-label continuation phase until dolutegravir is commercially approved.

| | |
|--|-------------------------------|
| Investigational medicinal product name | Abacavir/Lamivudine (ABC/3TC) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600/300 mg tablet once daily for 48 weeks in open-label phase (96 weeks through 144 week), and during open-label continuation phase until dolutegravir is commercially approved.

| | |
|------------------|---------------------------------------|
| Arm title | EFV/TDF/FTC 600/200/300 mg once daily |
|------------------|---------------------------------------|

Arm description:

Participants who completed double-blind phase continued to receive EFV/TDF/FTC 600/200/300 mg OD for additional 48 weeks during open-label phase.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600/200/300 mg tablet once daily for 48 weeks in open-label phase (96 weeks through 144 week).

| Number of subjects in period 2^[2] | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily |
|---|--|---------------------------------------|
| Started | 341 | 309 |
| Completed | 317 | 278 |
| Not completed | 24 | 31 |
| Consent withdrawn by subject | 3 | 7 |

| | | |
|--------------------------|---|----|
| Physician decision | - | 2 |
| Adverse event, non-fatal | 3 | 10 |
| Lost to follow-up | 8 | 8 |
| Lack of efficacy | 7 | 2 |
| Protocol deviation | 3 | 2 |

Notes:

[2] - 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: One subject in each treatment group elected not to enter the Open-label phase; however, they are considered to have completed the study.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |
|-----------------------|--|

Reporting group description:

During double-blind phase, participants received a dolutegravir (DTG) 50 milligram (mg) tablet along with an Abacavir/Lamivudine (ABC/3TC) 600/300 mg tablet once daily (OD) orally, with placebo to match Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) 600/200/300 mg for 96 weeks.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | EFV/TDF/FTC 600/200/300 mg once daily |
|-----------------------|---------------------------------------|

Reporting group description:

During double-blind phase, participants received EFV/TDF/FTC 600/200/300 mg OD, with placebo to match DTG 50 mg and ABC/3TC 600/300 mg for 96 weeks.

| Reporting group values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | Total |
|------------------------------------|--|---------------------------------------|-------|
| Number of subjects | 414 | 419 | 833 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 36.5 ± 10.74 | 36.4 ± 10.43 | - |
| Gender categorical Units: Subjects | | | |
| Female | 67 | 63 | 130 |
| Male | 347 | 356 | 703 |
| Race Units: Subjects | | | |
| African American (Af Am)/African Heritage (Af Ht) | 98 | 99 | 197 |
| American Indian (AI) or Alaska Native (Nat) | 13 | 17 | 30 |
| Asian | 9 | 9 | 18 |
| White | 284 | 285 | 569 |
| Af Am/Af Ht & AI or Alaska Native | 0 | 1 | 1 |
| Af Am/Af Ht & Nat Hawaiian/other Pacific Islander | 0 | 1 | 1 |
| Af Am/Af Ht & White | 3 | 2 | 5 |
| American Indian or Alaska Native & White | 6 | 4 | 10 |
| Asian & White | 1 | 0 | 1 |
| Missing | 0 | 1 | 1 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |
| Reporting group description: During double-blind phase, participants received a dolutegravir (DTG) 50 milligram (mg) tablet along with an Abacavir/Lamivudine (ABC/3TC) 600/300 mg tablet once daily (OD) orally, with placebo to match Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) 600/200/300 mg for 96 weeks. | |
| Reporting group title | EFV/TDF/FTC 600/200/300 mg once daily |
| Reporting group description: During double-blind phase, participants received EFV/TDF/FTC 600/200/300 mg OD, with placebo to match DTG 50 mg and ABC/3TC 600/300 mg for 96 weeks. | |
| Reporting group title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |
| Reporting group description: Participants who completed double-blind phase continued to receive DTG 50 mg tablet along with ABC/3TC 600/300 mg tablet OD orally, for additional 48 weeks during open-label phase. | |
| Reporting group title | EFV/TDF/FTC 600/200/300 mg once daily |
| Reporting group description: Participants who completed double-blind phase continued to receive EFV/TDF/FTC 600/200/300 mg OD for additional 48 weeks during open-label phase. | |
| Subject analysis set title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: During double-blind phase, participants received a dolutegravir (DTG) 50 milligram (mg) tablet along with an Abacavir/Lamivudine (ABC/3TC) 600/300 mg tablet once daily (OD) orally, with placebo to match Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) 600/200/300 mg for 96 weeks. Participants who completed double-blind phase continued to receive DTG 50 mg tablet along with ABC/3TC 600/300 mg tablet OD orally, for additional 48 weeks during open-label phase. | |
| Subject analysis set title | EFV/TDF/FTC 600/200/300 mg once daily |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: During double-blind phase, participants received EFV/TDF/FTC 600/200/300 mg OD, with placebo to match DTG 50 mg and ABC/3TC 600/300 mg for 96 weeks. Participants who completed double-blind phase continued to receive EFV/TDF/FTC 600/200/300 mg OD for additional 48 weeks during open-label phase. | |

Primary: Proportion of Subjects Responding based on Plasma HIV-1 RNA <50 c/mL at Week 48

| | |
|---|---|
| End point title | Proportion of Subjects Responding based on Plasma HIV-1 RNA <50 c/mL at Week 48 |
| End point description: The percentage of participants with plasma HIV-1 RNA <50 c/mL at Week 48 was assessed. Plasma samples were collected for the quantitative assessment of HIV-1 RNA based on the Missing, Switch, or Discontinuation equals Failure (MSDF) algorithm, as codified by the Food and Drug Administration's Snapshot algorithm. This algorithm treats all participants without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of investigational product prior to the visit window) as non-responders, as well as participants who switched their concomitant antiretroviral therapy (ART) in certain scenarios. Since changes in ART were not permitted in this protocol, all such participants who changed ART were to be considered non-responders. Otherwise, virologic success or failure was to be determined by the last available HIV-1 RNA assessment while the participant was on treatment within the visit of interest window. Intent-to-Treat-Exposed (ITT-E) Population. | |
| End point type | Primary |
| End point timeframe: Week 48 | |

| | | | | |
|-----------------------------------|--|---------------------------------------|--|--|
| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[1] | 419 ^[2] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 88 | 81 | | |

Notes:

[1] - ITT-E Population: all randomized par. who received at least one dose of study medication

[2] - ITT-E Population: all randomized par. who received at least one dose of study medication

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| The estimated value reflects the percentage on DTG + ABC/3TC minus the percentage on EFV/TDF/FTC. | |
| Comparison groups | DTG 50 mg plus ABC/3TC 600/300 mg once daily v EFV/TDF/FTC 600/200/300 mg once daily |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| P-value | = 0.003 ^[4] |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Difference in percentage |
| Point estimate | 7.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.3 |
| upper limit | 12.2 |

Notes:

[3] - Non-inferiority could be concluded if the lower bound of a two-sided 95% confidence interval for the difference (DTG + ABC/3TC minus EFV/TDF/FTC) in percentages between the two treatment arms was > -10%.

[4] - P-value is for the test of superiority.

Secondary: Time to viral suppression (<50 c/mL)

| | |
|--|--------------------------------------|
| End point title | Time to viral suppression (<50 c/mL) |
| End point description: | |
| Viral suppression is defined as the first viral load value <50 c/mL. The Kaplan-Meier method was used to estimate time to viral suppression, defined as the time from the first dose of study treatment until the first viral load value <50 c/mL was reached. Participants who withdrew for any reason without having suppressed prior to the analysis were censored. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline until Week 144) (average of 877.4 days for DTG; average of 788.8 study days for EFV/TDF/FTC) | |

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|----------------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[5] | 419 ^[6] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 28 (28 to 29) | 84 (83 to 84) | | |

Notes:

[5] - ITT-E Population

[6] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with plasma human immunodeficiency virus - 1 (HIV-1) ribonucleic acid (RNA) <50 copies/milliliter (c/mL) at Week 96 and Week 144

| | |
|-----------------|--|
| End point title | Percentage of participants with plasma human immunodeficiency virus -1 (HIV-1) ribonucleic acid (RNA) <50 copies/milliliter (c/mL) at Week 96 and Week 144 |
|-----------------|--|

End point description:

The percentage of participants with plasma HIV-1 RNA <50 c/mL at Week 96 and Week 144 was assessed. Plasma samples were collected for the quantitative assessment of HIV-1 RNA based on the Missing, Switch, or Discontinuation equals Failure (MSDF) algorithm, as codified by the Food and Drug Administration's Snapshot algorithm. This algorithm treats all participants without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of investigational product prior to the visit window) as non-responders, as well as participants who switched their concomitant antiretroviral therapy (ART) in certain scenarios. Since changes in ART were not permitted in this protocol, all such participants who changed ART were to be considered non-responders. Otherwise, virologic success or failure was to be determined by the last available HIV-1 RNA assessment while the participant was on treatment within the visit of interest window.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 96 and Week 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|-----------------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[7] | 419 ^[8] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 96 | 77 | 70 | | |
| Week 144 | 71 | 63 | | |

Notes:

[7] - ITT-E Population

[8] - ITT-E Population

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Week 96:The estimated value reflects the percentage on DTG + ABC/3TC minus the percentage on EFV/TDF/FTC. | |
| Comparison groups | DTG 50 mg plus ABC/3TC 600/300 mg once daily v EFV/TDF/FTC 600/200/300 mg once daily |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| P-value | = 0.016 ^[10] |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Difference in percentage |
| Point estimate | 7.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.2 |
| upper limit | 13.1 |

Notes:

[9] - Non-inferiority could be concluded if the lower bound of a two-sided 95% confidence interval for the difference (DTG + ABC/3TC minus EFV/TDF/FTC) in percentages between the two treatment arms was > -10%.

[10] - P-value is for the test of superiority.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Week 144:Estimated value reflects the percentage on DTG + ABC/3TC minus the percentage on EFV/TDF/FTC. | |
| Comparison groups | DTG 50 mg plus ABC/3TC 600/300 mg once daily v EFV/TDF/FTC 600/200/300 mg once daily |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[11] |
| P-value | = 0.01 ^[12] |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Difference in percentage |
| Point estimate | 8.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.9 |
| upper limit | 14.6 |

Notes:

[11] - Non-inferiority could be concluded if the lower bound of a two-sided 95% confidence interval for the difference (DTG + ABC/3TC minus EFV/TDF/FTC) in percentages between the two treatment arms was > -10%.

[12] - P-value is for the test of superiority.

Secondary: Number of participants with a confirmed plasma HIV-1 RNA level ≥ 1000 c/mL at or after Week 16 and before Week 24, or a confirmed plasma HIV-1 RNA level ≥ 200 c/mL at or after Week 24

| | |
|-----------------|---|
| End point title | Number of participants with a confirmed plasma HIV-1 RNA level ≥ 1000 c/mL at or after Week 16 and before Week 24, or a confirmed plasma HIV-1 RNA level ≥ 200 c/mL at or after Week 24 |
|-----------------|---|

End point description:

Data are presented as Kaplan Meier estimates of virologic failure (VF), defined as a confirmed plasma HIV-1 RNA level ≥ 1000 c/mL at or after Week 16 and before Week 24, or a confirmed plasma HIV-1 RNA level ≥ 200 c/mL at or after Week 24. A plasma HIV-1 RNA value was considered to be confirmed failure if a consecutive measurement satisfied the same failure criterion. The number of participants who experienced autoimmune deficiency syndrome (AIDS) Clinical Trials Group (ACTG) VFs was measured. For participants who withdrew from the study/were not documented to have reached confirmed VF at the cut off date of the Week 48 analysis, time to VF was to be censored at the planned visit week of the last measured plasma HIV-1 RNA sample. Data for participants who missed three consecutive scheduled plasma HIV-1 RNA measurements were to be censored at the planned visit week of the last assessment prior to the 3 consecutive missed visits.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline until Week 144) (average of 877.4 days for DTG; average of 788.8 study days for EFV/TDF/FTC)

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|-----------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[13] | 419 ^[14] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| ACTG virologic failures | 11 | 8 | | |
| Censored participants | 403 | 411 | | |

Notes:

[13] - ITT-E Population

[14] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in plasma HIV-1 RNA at Weeks 2, 4, 8, 12, 16, 24, 32, 40,48, 60, 72, 84, 96, 108, 120, 132 and 144

| | |
|-----------------|---|
| End point title | Change from Baseline in plasma HIV-1 RNA at Weeks 2, 4, 8, 12, 16, 24, 32, 40,48, 60, 72, 84, 96, 108, 120, 132 and 144 |
|-----------------|---|

End point description:

Blood samples were collected for the measurement of HIV-1 RNA in plasma. Changes from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants available at the indicated time points were assessed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[15] | 419 ^[16] | | |
| Units: log10 copies/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2, n=387, 376 | -2.46 (± 0.49) | -1.96 (± 0.46) | | |
| Week 4, n=404, 391 | -2.88 (± 0.58) | -2.25 (± 0.52) | | |
| Week 8, n=395, 386 | -2.99 (± 0.64) | -2.6 (± 0.6) | | |
| Week 12, n=394, 377 | -3.01 (± 0.7) | -2.85 (± 0.63) | | |
| Week 16, n=386, 366 | -3.03 (± 0.66) | -2.98 (± 0.65) | | |
| Week 24, n=389, 364 | -3.05 (± 0.69) | -3.01 (± 0.76) | | |
| Week 32, n=380, 355 | -3.04 (± 0.7) | -3.05 (± 0.72) | | |
| Week 40, n=370, 345 | -3.05 (± 0.68) | -3.04 (± 0.7) | | |
| Week 48, n=370, 343 | -3.03 (± 0.69) | -3.04 (± 0.69) | | |
| Week 60, n=360, 330 | -3.03 (± 0.67) | -3.05 (± 0.69) | | |
| Week 72, n=354, 320 | -3.03 (± 0.7) | -3.06 (± 0.7) | | |
| Week 84, n=353, 314 | -3.02 (± 0.7) | -3.07 (± 0.68) | | |
| Week 96, n=345, 310 | -2.99 (± 0.73) | -3.06 (± 0.68) | | |
| Week 108, n=340, 300 | -3.01 (± 0.71) | -3.08 (± 0.67) | | |
| Week 120, n=333, 289 | -3 (± 0.77) | -3.07 (± 0.67) | | |
| Week 132, n=323, 284 | -3.03 (± 0.68) | -3.06 (± 0.67) | | |
| Week 144, n=313, 269 | -3.02 (± 0.72) | -3.04 (± 0.69) | | |

Notes:

[15] - ITT-E Population

[16] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD4+ cell counts at Week 144

| | |
|-----------------|--|
| End point title | Change from Baseline in CD4+ cell counts at Week 144 |
|-----------------|--|

End point description:

Cluster of differentiation (CD4) lymphocyte cells (also called T-cells or T-helper cells) are the primary targets of HIV. The CD4 count and the CD4 percentage mark the degree of immunocompromise. The CD4 count is used to stage the patient's disease, determine the risk of opportunistic illnesses, assess prognosis, and guide decisions about when to start antiretroviral therapy. Change from Baseline was calculated as the Week 144 value minus the Baseline value. The least squares mean is the estimated mean change from Baseline in CD4+ cell counts at Week 144 calculated from a repeated measures model including the following covariates: treatment, visit, Baseline plasma HIV-1 RNA, Baseline CD4+ cell count, treatment*visit interaction, Baseline HIV-1 RNA*visit interaction, and Baseline CD4+ cell count*visit interaction. No assumptions were made about the correlations between a participant's readings of CD4+, i.e., the correlation matrix for within-participant errors is unstructured.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|---|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[17] | 419 ^[18] | | |
| Units: cells per millimeters cubed (cells/mm ³) | | | | |
| least squares mean (standard error) | 378.48 (± 10.99) | 331.57 (± 11.59) | | |

Notes:

[17] - ITT-E Population

[18] - ITT-E Population

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Comparison groups | DTG 50 mg plus ABC/3TC 600/300 mg once daily v EFV/TDF/FTC 600/200/300 mg once daily |
| Number of subjects included in analysis | 833 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[19] |
| P-value | = 0.003 ^[20] |
| Method | Repeated Measure Mixed Model |

Notes:

[19] - Adjusted mean is the estimated mean change from baseline (BL) in CD4 + Cell Count at Week 144 in each arm calculated from a repeated measures model including the following covariates: treatment, visit, BL plasma HIV-1 RNA, BL CD4 cell count, treatment*visit interaction, BL HIV-1 RNA*visit interaction and BL CD4 cell count*visit interaction. No assumptions were made about the correlations between a par.'s readings of CD4 i.e. the correlation matrix for within-subject errors is unstructured.

[20] - P-value is for the test of superiority.

Secondary: Change from Baseline in CD4+ cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144

| | |
|-----------------|---|
| End point title | Change from Baseline in CD4+ cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 |
|-----------------|---|

End point description:

CD4 lymphocyte cells (also called T-cells or T-helper cells) are the primary targets of HIV. The CD4 count and the CD4 percentage mark the degree of immunocompromise. The CD4 count is used to stage the patient's disease, determine the risk of opportunistic illnesses, assess prognosis, and guide decisions about when to start antiretroviral therapy. Change from Baseline was calculated as the value at Indicated visit minus the Baseline value. Only those participants available at the indicated time points were assessed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|---|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[21] | 419 ^[22] | | |
| Units: cells per millimeters cubed (cells/mm ³) | | | | |

| arithmetic mean (standard deviation) | | | | |
|--------------------------------------|------------------|------------------|--|--|
| Week 4, n=404,390 | 117.6 (± 114.51) | 80.9 (± 112.43) | | |
| Week 8, n=396,382 | 164.6 (± 129.98) | 124.4 (± 124.5) | | |
| Week 12, n=394,378 | 187.5 (± 157.46) | 153 (± 131.91) | | |
| Week 16, n=386,366 | 214.7 (± 173.35) | 174.1 (± 132.02) | | |
| Week 24, n=388,361 | 216.9 (± 162.89) | 177.8 (± 147.72) | | |
| Week 32, n=380,353 | 250.5 (± 172.06) | 208.1 (± 152.13) | | |
| Week 40, n=364,347 | 265.5 (± 187.81) | 216.2 (± 158.49) | | |
| Week 48, n=368,344 | 267.5 (± 192.3) | 209.5 (± 164.37) | | |
| Week 60, n=359,330 | 271.3 (± 188.05) | 235.3 (± 171.98) | | |
| Week 72, n=354,319 | 306.1 (± 202.02) | 269.6 (± 180.04) | | |
| Week 84, n=352,314 | 315.2 (± 197.92) | 272.1 (± 172.28) | | |
| Week 96, n=343,309 | 322.6 (± 205.35) | 286 (± 195.7) | | |
| Week 108, n=339,300 | 349.3 (± 218.76) | 298.9 (± 188.41) | | |
| Week 120, n=332,287 | 347 (± 234.96) | 311 (± 198.79) | | |
| Week 132, n=323,283 | 377.9 (± 205.78) | 327.2 (± 175.31) | | |
| Week 144, n=313,270 | 379.5 (± 221.17) | 333.3 (± 189.25) | | |

Notes:

[21] - ITT-E Population

[22] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated post-baseline HIV-associated conditions and progression, excluding recurrences at Week 144

| | |
|-----------------|--|
| End point title | Number of participants with the indicated post-baseline HIV-associated conditions and progression, excluding recurrences at Week 144 |
|-----------------|--|

End point description:

Clinical disease progression (CDP) was assessed according to the Centers for Disease Control and Prevention (CDC) HIV-1 classification system. Category (CAT) A: one or more of the following conditions (CON), without any CON listed in Categories B and C: asymptomatic HIV infection, persistent generalized lymphadenopathy, acute (primary) HIV infection with accompanying illness or history of acute HIV infection. CAT B: symptomatic CON that are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or that are considered by physicians to have a clinical course or to require management that is complicated by HIV infection; and not included among CON listed in clinical CAT C. CAT C: the clinical CON listed in the AIDS surveillance case definition. Indicators of CDP were defined as: CDC CAT A at Baseline (BS) to a CDC CAT C event (EV); CDC CAT B at BS to a CDC CAT C EV; CDC CAT C at BS to a new CDC CAT C EV; or CDC CAT A, B, or C at BS to death.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline until Week 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|--|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[23] | 419 ^[24] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Week 144, Any category condition | 17 | 24 | | |
| Week 144, Any Category B condition | 12 | 17 | | |
| Week 144, Any Category C condition | 5 | 6 | | |
| Week 144, Any death | 0 | 2 | | |
| Week 144, Progression from CAT A to CAT C | 4 | 4 | | |
| Week 144, Progression from CAT C to new CAT C | 1 | 2 | | |
| Week 144, Progression from CAT A, B, or C to death | 0 | 2 | | |

Notes:

[23] - ITT-E Population

[24] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Grade 1 to 4 clinical and hematology toxicities at Week 144

| | |
|-----------------|---|
| End point title | Number of participants with the indicated Grade 1 to 4 clinical and hematology toxicities at Week 144 |
|-----------------|---|

End point description:

All Grade 1 to 4 post-Baseline-emergent chemistry toxicities included alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), carbon dioxide (CO₂) content/bicarbonate, cholesterol, creatine kinase (CK), creatinine, hyperglycemia, hyperkalemia, hyponatremia, hypoglycemia, hypokalemia, hyponatremia, low density lipoprotein (LDL) cholesterol calculation, lipase, phosphorus inorganic, total bilirubin, and triglycerides. All Grade 1 to 4 post-Baseline-emergent hematology toxicities included hemoglobin, platelet count, total neutrophils, and white blood cell count. The Division of AIDS (DAIDS) defined toxicity grades as follows: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, potentially life threatening; Grade 5, death.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline until Week 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|-----------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[25] | 419 ^[26] | | |
| Units: Participants | | | | |

| | | | | |
|---------------------------------------|-----|-----|--|--|
| number (not applicable) | | | | |
| Week 144, ALT | 62 | 81 | | |
| Week 144, Albumin | 0 | 1 | | |
| Week 144, ALP | 17 | 53 | | |
| Week 144, AST | 77 | 85 | | |
| Week 144, CO2 content/bicarbonate | 135 | 134 | | |
| Week 144, Cholesterol | 156 | 140 | | |
| Week 144, CK | 91 | 79 | | |
| Week 144, Creatinine | 17 | 6 | | |
| Week 144, Hyperglycaemia | 121 | 105 | | |
| Week 144, Hyperkalemia | 4 | 12 | | |
| Week 144, Hyponatremia | 11 | 9 | | |
| Week 144, Hypoglycaemia | 24 | 21 | | |
| Week 144, Hypokalemia | 38 | 21 | | |
| Week 144, Hyponatremia | 63 | 86 | | |
| Week 144, LDL cholesterol calculation | 124 | 111 | | |
| Week 144, Lipase | 111 | 110 | | |
| Week 144, Phosphorus, inorganic | 109 | 134 | | |
| Week 144, Total bilirubin | 22 | 4 | | |
| Week 144, Triglycerides | 11 | 11 | | |
| Week 144, Hemoglobin | 7 | 11 | | |
| Week 144, Platelet count | 20 | 19 | | |
| Week 144, Total neutrophils | 70 | 80 | | |
| Week 144, White Blood Cell count | 9 | 18 | | |

Notes:

[25] - Safety Population: all participants who received at least one dose of investigational product

[26] - Safety Population: all participants who received at least one dose of investigational product

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated genotypic resistance with virological failure (VF) through Week 144

| | |
|-----------------|---|
| End point title | Number of participants with the indicated genotypic resistance with virological failure (VF) through Week 144 |
|-----------------|---|

End point description:

Whole blood samples were collected from participants to provide plasma for storage samples for potential viral genotypic and phenotypic analyses. Participants with confirmed virological failure (confirmed HIV-1 RNA ≥ 50 copies/mL throughout the study and/or confirmed HIV-1 RNA ≥ 200 copies/mL at Week 144) had plasma samples tested for HIV-1 RT genotype and HIV-1 integrase genotype from Baseline samples and from samples collected at the time of virological failure. Genotype testing was conducted at Day 1 and at the time of suspected protocol-defined virological failure (PDVF). A genotyping assessment was made of change across all amino acids within the integrase (IN)-encoding region, with particular attention paid to specific amino acid changes associated with the development of resistance to RAL, ELV, or DTG. PDVF Genotypic Population: all participants in the ITT-E Population with available on-treatment genotypic resistance data at the time of PDVF.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through Week 144

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|-------------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 26 ^[27] | 16 ^[28] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Week 144, RT mutation K65K/R | 0 | 1 | | |
| Week 144, RT mutation K101E | 0 | 1 | | |
| Week 144, RT mutation K103K/N | 0 | 2 | | |
| Week 144, RT mutation K103N | 0 | 2 | | |
| Week 144, RT mutation G190G/A | 0 | 2 | | |

Notes:

[27] - PDVF Genotypic Population

[28] - PDVF Genotypic Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Symptom Bother Score (SBS) at Week 4 through Week 48

| | |
|-----------------|--|
| End point title | Change from Baseline in the Symptom Bother Score (SBS) at Week 4 through Week 48 |
|-----------------|--|

End point description:

The Symptom Distress Module (SDM) is a 20-item, self-reported questionnaire measuring the presence/perceived distress linked to symptoms associated with HIV/its treatments. Developed with support from the AIDS Clinical Trials Group of the U.S. National Institute of Allergy and Infectious Diseases, it has demonstrated construct validity and has shown strong associations with physical/mental health summary scores and with disease severity. The SDM consists of 2 main scores: symptom count and the SBS, ranging from 0 (best) to 80 (worst) and based on the degree of bother that each symptom present posed. The SBS was calculated by adding the 20 individual bother item scores, which were calculated as: 0, "I do not have this symptom"; 1, "It doesn't bother me"; 2, "It bothers me a little"; 3, "It bothers me"; 4, "It bothers me a lot." Estimates are calculated from an analysis of covariance (ANCOVA) model adjusting for age, sex, race, Baseline (BL) viral load, BL CD4+ cell count, and BL SBS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 4 through 48

Par. with missing bother item scores at Week 4 had their last observation carried forward (LOCF). Only those par. contributing to the model (i.e., without missing response variables after LOCF or covariates) were analyzed.

| End point values | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | | |
|-------------------------------------|--|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 394 ^[29] | 393 ^[30] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -1.818 (± 0.3849) | -1.246 (± 0.3854) | | |

Notes:

[29] - ITT-E Population

[30] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication to Week 144 (average of 877.4 study days for DTG; average of 788.8 study days for EFV/TDF/FTC).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all participants who received at least one dose of investigational product.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | DTG 50 mg plus ABC/3TC 600/300 mg once daily |
|-----------------------|--|

Reporting group description:

During double-blind phase, participants received a dolutegravir (DTG) 50 milligram (mg) tablet along with an Abacavir/Lamivudine (ABC/3TC) 600/300 mg tablet once daily (OD) orally, with placebo to match Efavirenz/Tenofovir disoproxil fumarate/Emtricitabine (EFV/TDF/FTC) 600/200/300 mg for 96 weeks. Participants who completed double-blind phase continued to receive DTG 50 mg tablet along with ABC/3TC 600/300 mg tablet OD orally, for additional 48 weeks during open-label phase.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | EFV/TDF/FTC 600/200/300 mg once daily |
|-----------------------|---------------------------------------|

Reporting group description:

During double-blind phase, participants received EFV/TDF/FTC 600/200/300 mg OD, with placebo to match DTG 50 mg and ABC/3TC 600/300 mg for 96 weeks. Participants who completed double-blind phase continued to receive EFV/TDF/FTC 600/200/300 mg OD for additional 48 weeks during open-label phase.

| Serious adverse events | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 65 / 414 (15.70%) | 60 / 419 (14.32%) | |
| number of deaths (all causes) | 0 | 5 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hodgkin's disease | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancoast's tumour | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleomorphic adenoma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Bartholin's cyst | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Priapism | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pneumothorax spontaneous subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sleep apnoea syndrome subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillar disorder subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders Suicide attempt subjects affected / exposed | 3 / 414 (0.72%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression subjects affected / exposed | 1 / 414 (0.24%) | 3 / 419 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation subjects affected / exposed | 2 / 414 (0.48%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Homicidal ideation subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol abuse | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar I disorder | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug abuse | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination, visual | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mania | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervousness | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paranoia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Personality disorder | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Schizophrenia, paranoid type | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shared psychotic disorder | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal behaviour | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intentional overdose | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chemical burn of skin | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Forearm fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 3 / 419 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasogenic cerebral oedema | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cyst | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Basedow's disease | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Tendon disorder | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 4 / 414 (0.97%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 3 / 419 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 2 / 419 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 3 / 419 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syphilis | | | |
| subjects affected / exposed | 2 / 414 (0.48%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AIDS dementia complex | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis pharyngeal | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Human herpesvirus 6 infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected dermal cyst | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis cryptococcal | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mycobacterium avium complex infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurosyphilis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumococcal sepsis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scrotal abscess | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal abscess | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic candida | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxoplasmosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 414 (0.00%) | 1 / 419 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 414 (0.24%) | 0 / 419 (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 | DTG 50 mg plus ABC/3TC 600/300 mg once daily | EFV/TDF/FTC 600/200/300 mg once daily | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 332 / 414 (80.19%) | 358 / 419 (85.44%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Anogenital warts | | | |
| subjects affected / exposed | 23 / 414 (5.56%) | 17 / 419 (4.06%) | |
| occurrences (all) | 25 | 17 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 43 / 414 (10.39%) | 154 / 419 (36.75%) | |
| occurrences (all) | 49 | 177 | |
| Headache | | | |
| subjects affected / exposed | 67 / 414 (16.18%) | 64 / 419 (15.27%) | |
| occurrences (all) | 82 | 81 | |
| Somnolence | | | |
| subjects affected / exposed | 10 / 414 (2.42%) | 24 / 419 (5.73%) | |
| occurrences (all) | 12 | 25 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |

| | | | |
|--|--------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 67 / 414 (16.18%) 77 | 56 / 419 (13.37%) 64 | |
| Pyrexia subjects affected / exposed occurrences (all) | 27 / 414 (6.52%) 32 | 30 / 419 (7.16%) 31 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 94 / 414 (22.71%) 125 | 89 / 419 (21.24%) 109 | |
| Nausea subjects affected / exposed occurrences (all) | 70 / 414 (16.91%) 82 | 63 / 419 (15.04%) 68 | |
| Vomiting subjects affected / exposed occurrences (all) | 28 / 414 (6.76%) 34 | 27 / 419 (6.44%) 36 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 39 / 414 (9.42%) 43 | 40 / 419 (9.55%) 44 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 32 / 414 (7.73%) 39 | 19 / 419 (4.53%) 21 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 22 / 414 (5.31%) 24 | 63 / 419 (15.04%) 71 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 74 / 414 (17.87%) 89 | 52 / 419 (12.41%) 57 | |
| Abnormal dreams subjects affected / exposed occurrences (all) | 32 / 414 (7.73%) 34 | 74 / 419 (17.66%) 81 | |
| Depression subjects affected / exposed occurrences (all) | 34 / 414 (8.21%) 39 | 38 / 419 (9.07%) 40 | |

| | | | |
|---|--------------------------|--------------------------|--|
| Anxiety subjects affected / exposed occurrences (all) | 33 / 414 (7.97%) 38 | 35 / 419 (8.35%) 42 | |
| Nightmare subjects affected / exposed occurrences (all) | 11 / 414 (2.66%) 12 | 21 / 419 (5.01%) 26 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 37 / 414 (8.94%) 44 | 25 / 419 (5.97%) 27 | |
| Arthralgia subjects affected / exposed occurrences (all) | 28 / 414 (6.76%) 36 | 24 / 419 (5.73%) 31 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 23 / 414 (5.56%) 25 | 14 / 419 (3.34%) 14 | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 86 / 414 (20.77%) 137 | 81 / 419 (19.33%) 124 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 69 / 414 (16.67%) 95 | 58 / 419 (13.84%) 84 | |
| Bronchitis subjects affected / exposed occurrences (all) | 33 / 414 (7.97%) 39 | 33 / 419 (7.88%) 37 | |
| Syphilis subjects affected / exposed occurrences (all) | 26 / 414 (6.28%) 28 | 31 / 419 (7.40%) 33 | |
| Sinusitis subjects affected / exposed occurrences (all) | 29 / 414 (7.00%) 35 | 18 / 419 (4.30%) 21 | |
| Influenza subjects affected / exposed occurrences (all) | 31 / 414 (7.49%) 35 | 14 / 419 (3.34%) 15 | |
| Gastroenteritis | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 26 / 414 (6.28%) | 18 / 419 (4.30%) | |
| occurrences (all) | 28 | 22 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 29 October 2010 | Country Specific Amendment for the United Kingdom |
| 14 January 2011 | This amendment includes the addition of standard hematology and clinical chemistry laboratory assessments as being required for all subjects at the Week 2 study visit. Minor clarifications and corrections have been incorporated. |
| 10 October 2011 | This amendment allows for a change in the management of subjects with protocol-defined virologic failure. Additional follow-up assessments were added to the Liver Chemistry Stopping criteria panel. Planned exploratory bone biomarkers results will not be reported to investigators with one exception. |
| 01 August 2012 | This amendment adds an Open-label Randomized Phase to both treatment arms from Week 96 to Week 144 to collect long term efficacy and safety data. |
| 17 August 2012 | This amendment enables the use of both the commercial presentation of Atripla and the overcoated Atripla in the Open-label Randomized Phase from Week 96 to Week 144. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported