



Clinical trial results:

A Phase III study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1 infected adult subjects with treatment failure on an integrase inhibitor containing regimen.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-017951-87 |
| Trial protocol | BE PT IT ES |
| Global end of trial date | 25 May 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 12 May 2016 |
| First version publication date | 12 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 112574 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, +1 8664357343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, +1 8664357343, |

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? | |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 August 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 May 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to assess the antiviral activity and safety of a dolutegravir (DTG) containing regimen in HIV-1 infected, antiretroviral therapy (ART)-experienced adults with current or historical failure on an integrase inhibitor (INI) containing regimen. The study will assess DTG 50mg twice daily administered initially with the current failing ART regimen but then with an optimised background ART regimen (OBR) after Day 7. The first analyses will be conducted after the last subject enrolled has completed 24 weeks. Subjects may remain on study after Week 24.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 06 May 2011 |
| 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 | Belgium: 1 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | France: 38 |
| Country: Number of subjects enrolled | Italy: 30 |
| Country: Number of subjects enrolled | Portugal: 6 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | United States: 99 |
| Worldwide total number of subjects | 183 |
| EEA total number of subjects | 81 |

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 | 0 |

| | |
|---------------------------|-----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 179 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants (par.) having documented Human immunodeficiency virus type 1 (HIV-1) infection with a plasma HIV-1 Ribonucleic acid(RNA) ≥ 500 copies per milliliter (c/mL) at Screening, Antiretroviral therapy (ART)-experienced and on stable ART for at least one month prior to Screening were enrolled

Pre-assignment

Screening details:

A total of 139 par. were screen failures and 183 par. entered the single arm, open-label study.

Period 1

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

Arms

| | |
|------------------|------------------------|
| Arm title | Dolutegravir 50 mg BID |
|------------------|------------------------|

Arm description:

Participants received dolutegravir (DTG) 50 milligrams (mg) twice a day (BID).

| | |
|--|--------------|
| 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:

1 X 50mg tablet twice daily, Tablet for oral use

| Number of subjects in period 1 | Dolutegravir 50 mg BID |
|--------------------------------|------------------------|
| Started | 183 |
| Completed | 126 |
| Not completed | 57 |
| Physician decision | 2 |
| Consent withdrawn by subject | 7 |
| Adverse event, non-fatal | 7 |
| Lost to follow-up | 7 |
| Lack of efficacy | 27 |
| Protocol deviation | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 183 | 183 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| median | 48 | | |
| full range (min-max) | 19 to 67 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 42 | 42 | |
| Male | 141 | 141 | |
| Race | | | |
| Units: Subjects | | | |
| African American/African Heritage | 49 | 49 | |
| American Indian or Alaska Native and White | 1 | 1 | |
| Asian-Central/South Asian Heritage | 1 | 1 | |
| White | 130 | 130 | |
| White and African American/African Heritage | 2 | 2 | |

End points

End points reporting groups

| | |
|--|------------------------|
| Reporting group title | Dolutegravir 50 mg BID |
| Reporting group description: | |
| Participants received dolutegravir (DTG) 50 milligrams (mg) twice a day (BID). | |

Primary: Mean change from Baseline in Plasma HIV-1 RNA at Day 8

| | |
|-----------------|---|
| End point title | Mean change from Baseline in Plasma HIV-1 RNA at Day 8 ^[1] |
|-----------------|---|

End point description:

Mean change from Baseline in Plasma Human Immunodeficiency Virus-1 (HIV-1) Ribonucleic Acid (RNA) at Day 8 was calculated as the Day 8 value minus the Baseline value. The last observation was carried forward if a participant had missed the Day 8 visit. The Baseline observation was carried forward if a participant had discontinued the treatment before Day 8. Blood samples for assessment of HIV-1 RNA levels were collected at Baseline and Day 8. The P-value (< 0.001) was derived by the null hypothesis testing of no change from Baseline in HIV-1 RNA at Day 8 at the two-sided 5% significance level using a single sample 2 sided, t-test. Change from baseline (-1.432) and 2 sided 95% confidence interval (-1.520 to -1.343) was calculated using T distribution. Intent-to-Treat-Exposed (ITT-E) Population is defined as all participants who received at least one dose of study drug. Only participants who had Day 8 observations were considered for analysis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Day 8

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: There are no statistical data to report.

| End point values | Dolutegravir 50 mg BID | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 182 ^[2] | | | |
| Units: log10 copies/milliliter (mL) | | | | |
| arithmetic mean (standard deviation) | -1.432 (\pm 0.607) | | | |

Notes:

[2] - Intent-to-treat-Exposed Population. One participant did not have a Day 8 visit.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with HIV-1 RNA less than 50 copies (c)/mL at Week 24

| | |
|-----------------|--|
| End point title | Number of participants with HIV-1 RNA less than 50 copies (c)/mL at Week 24 ^[3] |
|-----------------|--|

End point description:

The number of par. who had viral load < 50 c/mL at Week 24 based on the Food and Drug Administration's Snapshot algorithm was assessed. This algorithm treats all par. without HIV-1 RNA data at the visit of interest (VOI [due to missing data/discontinuation of investigational product prior to the visit window]) as nonresponders, as well as par. who switched their concomitant antiretroviral (ART) prior to the VOI as follows: background ART substitutions not permitted per protocol; background ART substitutions permitted per protocol, however the decision to switch was not documented as being

before or at the first on-treatment visit after switching to optimized background regimen (i.e., Week 4) where HIV-1 RNA was assessed. Otherwise, virologic success/failure was to be determined by the last available HIV-1 RNA assessment while the par. was on treatment within the VOI analysis window. The percentage of par. with HIV-1 RNA <50 c/mL at week 24 was 69% with 2 sided 95% CI as 62% to 76%.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Week 24 | |

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: There are no statistical data to report.

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[4] | | | |
| Units: participants | | | | |
| number (not applicable) | 126 | | | |

Notes:

[4] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with HIV-1 RNA less than 50 copies(c)/mL at Week 48

| | |
|-----------------|---|
| End point title | Number of participants with HIV-1 RNA less than 50 copies(c)/mL at Week 48 ^[5] |
|-----------------|---|

End point description:

The number of participants who had viral load <50 c/mL at Week 48 based on the Food and Drug Administration's Snapshot algorithm was assessed. This algorithm treats all participants without HIV-1 RNA data at the VOI (due to missing data/discontinuation of investigational product prior to the visit window) as non responders, as well as participants who switched their concomitant ART prior to the VOI as follows: background ART substitutions not permitted per protocol; background ART substitutions permitted per protocol, however the decision to switch was not documented as being before or at the first on-treatment visit after switching to optimized background regimen (i.e., Week 4) where HIV-1 RNA was assessed. Otherwise, virologic success/failure was to be determined by the last available HIV-1 RNA assessment while the participant was on treatment within the VOI analysis window. The percentage of participants with HIV-1 RNA <50 c/mL at Week 48 was 63% with 2 sided 95% CI as 56% to 70%.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Week 48 | |

Notes:

[5] - 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: There are no statistical data to report.

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[6] | | | |
| Units: participants | | | | |
| number (not applicable) | 116 | | | |

Notes:

[6] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with any Adverse Event (AE) or any serious adverse event (SAE)

| | |
|-----------------|--|
| End point title | Number of participants with any Adverse Event (AE) or any serious adverse event (SAE) ^[7] |
|-----------------|--|

End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

Notes:

[7] - 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: There are no statistical data to report.

| End point values | Dolutegravir 50 mg BID | | | |
|-----------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[8] | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Any AE | 169 | | | |
| Any SAE | 46 | | | |

Notes:

[8] - Safety Population: all participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Adverse Events of the indicated severity, per the Division of Acquired Immune Deficiency Syndrome (DAIDS) grading scale

| | |
|-----------------|--|
| End point title | Number of participants with Adverse Events of the indicated severity, per the Division of Acquired Immune Deficiency Syndrome (DAIDS) grading scale ^[9] |
|-----------------|--|

End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the

medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. AE/SAE severity was graded according to the DAIDS grading scale. The DAIDS displays events as Grades 1-4 based on this general guideline: Grade (G) 1, mild; G2, moderate; G3, severe; G4, potentially life threatening.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

Notes:

[9] - 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: There are no statistical data to report.

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[10] | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Grade 1 | 45 | | | |
| Grade 2 | 64 | | | |
| Grade 3 | 44 | | | |
| Grade 4 | 16 | | | |

Notes:

[10] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the maximum post-Baseline-emergent clinical chemistry toxicities of the indicated grade

| | |
|-----------------|---|
| End point title | Number of participants with the maximum post-Baseline-emergent clinical chemistry toxicities of the indicated grade ^[11] |
|-----------------|---|

End point description:

The severity of clinical chemistry toxicities was graded according to the DAIDS toxicity scale. The DAIDS displays events as Grades 1-5 based on this general guideline: Grade (G) 1, mild; G2, moderate; G3, severe; G4, life threatening; G5, death related to toxicity.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

Notes:

[11] - 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: There are no statistical data to report.

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[12] | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Grade 1 | 49 | | | |
| Grade 2 | 67 | | | |
| Grade 3 | 43 | | | |
| Grade 4 | 16 | | | |

Notes:

[12] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the maximum post-Baseline-emergent hematology toxicities of the indicated grade

| | |
|-----------------|---|
| End point title | Number of participants with the maximum post-Baseline-emergent hematology toxicities of the indicated grade ^[13] |
|-----------------|---|

End point description:

The severity of hematology toxicities was graded according to the DAIDS. The DAIDS displays events as Grades 1-5 based on this general guideline: Grade (G) 1, mild; G2, moderate; G3, severe; G4, life threatening; G5, death related to toxicity.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

Notes:

[13] - 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: There are no statistical data to report.

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[14] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Grade 1 | 31 | | | |
| Grade 2 | 15 | | | |
| Grade 3 | 4 | | | |
| Grade 4 | 2 | | | |

Notes:

[14] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with plasma HIV-1 RNA less than 400 and 50 copies/mL at Baseline; Day 8; and Weeks 4, 8, 12, 16, 24, 32, 40, and 48

| | |
|---|--|
| End point title | Number of participants with plasma HIV-1 RNA less than 400 and 50 copies/mL at Baseline; Day 8; and Weeks 4, 8, 12, 16, 24, 32, 40, and 48 |
| End point description: | |
| The number of participants with plasma HIV-1 RNA less than 400 and 50 copies (c)/mL at Baseline; Day 8; and Weeks 4, 8, 12, 16, 24, 32, 40 and 48 based on the Food and Drug Administration's Snapshot algorithm was assessed. This algorithm treats all participants without HIV-1 RNA data at the visit of interest (VOI [due to missing data/discontinuation of investigational product prior to the visit window]) as nonresponders, as well as participants who switched their concomitant antiretroviral (ART) prior to the VOI as follows: background ART substitutions not permitted per protocol; background ART substitutions permitted per protocol, however the decision to switch was not documented as being before or at the first on-treatment visit after switching to optimized background regimen (i.e., Week 4) where HIV-1 RNA was assessed. Otherwise, virologic success/failure was to be determined by the last available HIV-1 RNA assessment while the par. was on treatment within the VOI analysis window | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Day 8; and Weeks 4, 8, 12, 16, 24, 32, 40, and 48 | |

| End point values | Dolutegravir 50 mg BID | | | |
|-------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[15] | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| HIV-1 RNA <50 c/mL, Baseline | 1 | | | |
| HIV-1 RNA <50 c/mL, Day 8 | 28 | | | |
| HIV-1 RNA <50 c/mL, Week 4 | 98 | | | |
| HIV-1 RNA <50 c/mL, Week 8 | 112 | | | |
| HIV-1 RNA <50 c/mL, Week 12 | 116 | | | |
| HIV-1 RNA <50 c/mL, Week 16 | 116 | | | |
| HIV-1 RNA <50 c/mL, Week 24 | 126 | | | |
| HIV-1 RNA <50 c/mL, Week 32 | 117 | | | |
| HIV-1 RNA <50 c/mL, Week 40 | 108 | | | |
| HIV-1 RNA <50 c/mL, Week 48 | 116 | | | |
| HIV-1 RNA <400 c/mL, Baseline | 8 | | | |
| HIV-1 RNA <400 c/mL, Day 8 | 82 | | | |
| HIV-1 RNA <400 c/mL, Week 4 | 145 | | | |
| HIV-1 RNA <400 c/mL, Week 8 | 146 | | | |
| HIV-1 RNA <400 c/mL, Week 12 | 142 | | | |
| HIV-1 RNA <400 c/mL, Week 16 | 139 | | | |
| HIV-1 RNA <400 c/mL, Week 24 | 135 | | | |
| HIV-1 RNA <400 c/mL, Week 32 | 127 | | | |
| HIV-1 RNA <400 c/mL, Week 40 | 119 | | | |
| HIV-1 RNA <400 c/mL, Week 48 | 125 | | | |

Notes:

[15] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with plasma HIV-1 RNA less than 400 and 50

copies/mL from Week 48 every 12 weeks up to study completion

| | |
|-----------------|--|
| End point title | Number of participants with plasma HIV-1 RNA less than 400 and 50 copies/mL from Week 48 every 12 weeks up to study completion |
|-----------------|--|

End point description:

The number of participants with plasma HIV-1 RNA less than 400 and 50 copies (c)/mL was assessed at Weeks 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168 and 180 using data of observed cases. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). Intention to treat-Exposed (ITT-E) population was defined as only those participants with data available at the indicated time points were considered for analysis (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT-E Population.

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

End point timeframe:

From Week 48 every 12 weeks up to study completion.

| End point values | Dolutegravir 50 mg BID | | | |
|-------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[16] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| HIV-1 RNA <50 c/mL, Week 48, n =146 | 121 | | | |
| HIV-1 RNA <50 c/mL, Week 60, n=142 | 110 | | | |
| HIV-1 RNA <50 c/mL, Week 72, n=138 | 116 | | | |
| HIV-1 RNA <50 c/mL, Week 84, n=138 | 108 | | | |
| HIV-1 RNA <50 c/mL, Week 96, n=120 | 101 | | | |
| HIV-1 RNA <50 c/mL, Week 108, n=98 | 81 | | | |
| HIV-1 RNA <50 c/mL, Week 120, n=82 | 72 | | | |
| HIV-1 RNA <50 c/mL, Week 132, n=61 | 49 | | | |
| HIV-1 RNA <50 c/mL, Week 144, n=45 | 37 | | | |
| HIV-1 RNA <50 c/mL, Week 156, n=32 | 28 | | | |
| HIV-1 RNA <50 c/mL, Week 168, n=24 | 20 | | | |
| HIV-1 RNA <50 c/mL, Week 180, n=6 | 4 | | | |
| HIV-1 RNA <400 c/mL, Week 48, n=146 | 134 | | | |
| HIV-1 RNA <400 c/mL, Week 60, n=142 | 131 | | | |
| HIV-1 RNA <400 c/mL, Week 72, n=138 | 130 | | | |
| HIV-1 RNA <400 c/mL, Week 84, n=138 | 127 | | | |
| HIV-1 RNA <400 c/mL, Week 96, n=120 | 111 | | | |
| HIV-1 RNA <400 c/mL, Week 108, n=98 | 92 | | | |
| HIV-1 RNA <400 c/mL, Week 120, n=82 | 80 | | | |
| HIV-1 RNA <400 c/mL, Week 132, n=61 | 59 | | | |
| HIV-1 RNA <400 c/mL, Week 144, n=45 | 44 | | | |
| HIV-1 RNA <400 c/mL, Week 156, n=32 | 31 | | | |
| HIV-1 RNA <400 c/mL, Week 168, n=24 | 23 | | | |
| HIV-1 RNA <400 c/mL, Week 180, n=6 | 5 | | | |

Notes:

[16] - ITT-E Population

Statistical analyses

Secondary: Mean change from Baseline in plasma HIV-1 RNA at Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and from Week 48 every 12 weeks up to study completion

| | |
|-----------------|---|
| End point title | Mean change from Baseline in plasma HIV-1 RNA at Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and from Week 48 every 12 weeks up to study completion |
|-----------------|---|

End point description:

Mean change from Baseline in plasma HIV-1 RNA was assessed at Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, and 180 using data of the observed cases. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Intention to treat-Exposed (ITT-E) population was defined as only those participants with data available at the indicated time points were considered for analysis (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT-E Population.

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

End point timeframe:

Baseline; Day 8; Weeks 4, 8, 12, 16, 24, 32, 40, and From Week 48 Every 12 Weeks up to Study completion (Up to Week 180)

| End point values | Dolutegravir 50 mg BID | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[17] | | | |
| Units: Log10 copies/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8, n=182 | -1.432 (± 0.607) | | | |
| Week 4, n=180 | -2.088 (± 0.885) | | | |
| Week 8, n=179 | -2.101 (± 0.987) | | | |
| Week 12, n=174 | -2.113 (± 1.069) | | | |
| Week 16, n=165 | -2.216 (± 1.005) | | | |
| Week 24, n=164 | -2.211 (± 1.023) | | | |
| Week 32, n=146 | -2.373 (± 0.926) | | | |
| Week 40, n=144 | -2.301 (± 0.955) | | | |
| Week 48, n=146 | -2.321 (± 0.981) | | | |
| Week 60, n=142 | -2.356 (± 0.928) | | | |
| Week 72, n=138 | -2.39 (± 0.941) | | | |
| Week 84, n=138 | -2.311 (± 0.996) | | | |
| Week 96, n=120 | -2.346 (± 1.008) | | | |
| Week 108, n=98 | -2.394 (± 0.966) | | | |
| Week 120, n=82 | -2.515 (± 0.904) | | | |

| | | | | |
|----------------|------------------|--|--|--|
| Week 132, n=61 | -2.456 (± 0.988) | | | |
| Week 144, n=45 | -2.585 (± 0.983) | | | |
| Week 156, n=32 | -2.595 (± 1.009) | | | |
| Week 168, n=24 | -2.719 (± 0.898) | | | |
| Week 180, n=6 | -2.425 (± 1.557) | | | |

Notes:

[17] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values for CD4+ cell counts at Baseline, Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and 48 and for CD8+ cell counts at Baseline and Weeks 4, 12, 24, and 48

| | |
|-----------------|---|
| End point title | Absolute values for CD4+ cell counts at Baseline, Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and 48 and for CD8+ cell counts at Baseline and Weeks 4, 12, 24, and 48 |
|-----------------|---|

End point description:

Absolute values for CD4+ cell counts were assessed at Baseline, Day 8 and Weeks 4, 8, 12, 16, and 24, and absolute values for CD8+ cell counts were assessed at Baseline and Weeks 4, 12, 24, and 48. Only those participants with data available at the indicated time points were considered for analysis (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT-E Population.

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

End point timeframe:

Baseline, Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and 48

| End point values | Dolutegravir 50 mg BID | | | |
|---|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[18] | | | |
| Units: Cells per millimeters cubed (cells/mm ³) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| CD4+, Baseline, n=183 | 140 (40 to 330) | | | |
| CD4+, Day 8, n=181 | 170 (60 to 350) | | | |
| CD4+, Week 4, n=178 | 185 (80 to 350) | | | |
| CD4+, Week 8, n=178 | 210 (100 to 350) | | | |
| CD4+, Week 12, n=171 | 210 (110 to 360) | | | |
| CD4+, Week 16, n=165 | 210 (130 to 400) | | | |
| CD4+, Week 24, n=163 | 250 (130 to 420) | | | |

| | | | | |
|----------------------|--------------------|--|--|--|
| CD4+, Week 32, n=147 | 270 (170 to 440) | | | |
| CD4+, Week 40, n=143 | 290 (200 to 440) | | | |
| CD4+, Week 48, n=145 | 310 (200 to 450) | | | |
| CD8+, Week 4, n=181 | 860 (540 to 1220) | | | |
| CD8+, Week 4, n=176 | 970 (655 to 1405) | | | |
| CD8+, Week 12, n=170 | 1015 (730 to 1460) | | | |
| CD8+, Week 24, n=154 | 1020 (690 to 1460) | | | |
| CD8+, Week 48, n=140 | 1000 (720 to 1380) | | | |

Notes:

[18] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median change from Baseline in CD4+ cell counts at Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and from Week 48 every 12 weeks until study completion

| | |
|-----------------|---|
| End point title | Median change from Baseline in CD4+ cell counts at Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, and from Week 48 every 12 weeks until study completion |
|-----------------|---|

End point description:

Median change from Baseline in CD4+ cell counts was assessed at Day 8 and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, and 180. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants with data available at the indicated time points were considered for analysis (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT-E Population.

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

End point timeframe:

Baseline; Day 8; Weeks 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168 and 180.

| | | | | |
|---|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[19] | | | |
| Units: Cells per millimeters cubed (cells/mm ³) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| CD4+, Day 8, n=181 | 20 (0 to 60) | | | |
| CD4+, Week 4, n=178 | 30 (0 to 71) | | | |
| CD4+, Week 8, n=178 | 40 (0 to 81) | | | |
| CD4+, Week 12, n=171 | 50 (0 to 100) | | | |
| CD4+, Week 16, n=165 | 60 (20 to 130) | | | |
| CD4+, Week 24, n=163 | 61 (20 to 130) | | | |

| | | | | |
|----------------------|--------------------|--|--|--|
| CD4+, Week 32, n=147 | 100 (20 to 160) | | | |
| CD4+, Week 40, n=143 | 90 (30 to 180) | | | |
| CD4+, Week 48, n=145 | 110 (40 to 190) | | | |
| CD4+, Week 60, n=142 | 120 (50 to 210) | | | |
| CD4+, Week 72, n=138 | 140 (60 to 231) | | | |
| CD4+, Week 84, n=137 | 150 (80 to 240) | | | |
| CD4+, Week 96, n=117 | 160 (80 to 270) | | | |
| CD4+, Week 108, n=98 | 180.5 (80 to 280) | | | |
| CD4+, Week 120, n=82 | 180 (100 to 280) | | | |
| CD4+, Week 132, n=61 | 221 (100 to 320) | | | |
| CD4+, Week 144, n=46 | 205 (130 to 350) | | | |
| CD4+, Week 156, n=32 | 225 (155 to 345) | | | |
| CD4+, Week 168, n=24 | 265 (155 to 380) | | | |
| CD4+, Week 180, n=6 | 170.5 (140 to 230) | | | |

Notes:

[19] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of CD4+/CD8+ cell count at Baseline and Weeks 4, 12, 24, and 48

| | |
|--|---|
| End point title | Ratio of CD4+/CD8+ cell count at Baseline and Weeks 4, 12, 24, and 48 |
| End point description: The ratio of CD4+/CD8+ cell count (measured in cells/mm^3) was assessed at Baseline and at Weeks 4, 12, 24, and 48. The ratio was calculated as the CD4+ cell count divided by CD8+ cell count. Only those participants with data available at the indicated time points were considered for analysis (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT-E Population. | |
| End point type | Secondary |
| End point timeframe: Baseline; Weeks 4, 12, 24, and 48 | |

| | | | | |
|---------------------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[20] | | | |
| Units: ratio | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Baseline, n=180 | 0.15 (0.05 to 0.34) | | | |

| | | | | |
|----------------|---------------------|--|--|--|
| Week 4, n=176 | 0.19 (0.09 to 0.37) | | | |
| Week 12, n=170 | 0.21 (0.1 to 0.46) | | | |
| Week 24, n=154 | 0.26 (0.14 to 0.46) | | | |
| Week 48, n=140 | 0.32 (0.19 to 0.52) | | | |

Notes:

[20] - ITT-E population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with HIV-1 disease progression (Acquired Immune Deficiency Syndrome [AIDS] or death)

| | |
|-----------------|---|
| End point title | Number of participants with HIV-1 disease progression (Acquired Immune Deficiency Syndrome [AIDS] or death) |
|-----------------|---|

End point description:

The number of participants with HIV-1 disease progression (AIDS or death) was assessed per the Centers for Disease Control and Prevention (CDC) 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. The CDC classifies HIV infection as Category A (participants with asymptomatic HIV infection, acute HIV infection with accompanying illness, or persistent generalized lymphadenopathy), Category B (participants with symptomatic non-AIDS condition, i.e., conditions that are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection), and Category C (includes AIDS indicator conditions as defined by diagnostic or presumptive measures).

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

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

| | | | | |
|---|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[21] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Progression from CDC Class A to Class C Event | 1 | | | |
| Progression from CDC Class B to Class C Event | 2 | | | |
| Progression from CDC Class C to New Class C Event | 6 | | | |
| Progression from Classes A, B, or C to Death | 2 | | | |

Notes:

[21] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax and Ctau of DTG

| | |
|-----------------|----------------------|
| End point title | Cmax and Ctau of DTG |
|-----------------|----------------------|

End point description:

The maximum plasma concentration (Cmax) and the concentration at the end of a dosing interval (Ctau) of DTG were assessed by a population pharmacokinetic (PK) modeling approach using pooled DTG PK data from multiple studies. For this study, blood samples for pharmacokinetic assessments were collected pre-dose on Day 8 and at Weeks 4 and 24, at 1-3 hours post-dose on Day 8, and at 1-3 hours or 4-12 hours post-dose at Weeks 4 and 24. The Pharmacokinetic (PK) Concentration Population used is defined as all subjects who received DTG, had undergone PK sampling during the study, and provided evaluable DTG plasma concentration data.

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

End point timeframe:

Day 8, Week 4, and Week 24

| End point values | Dolutegravir 50 mg BID | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[22] | | | |
| Units: Micrograms per milliliter (µg/mL) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Cmax | 4.74 (4.18 to 5.36) | | | |
| Ctau | 2.6 (2.15 to 3.15) | | | |

Notes:

[22] - The Pharmacokinetic (PK) Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-tau) and AUC(0-24) of DTG

| | |
|-----------------|---------------------------------|
| End point title | AUC(0-tau) and AUC(0-24) of DTG |
|-----------------|---------------------------------|

End point description:

The area under the time concentration curve over the dosing interval (AUC[0-tau]) and from 0 to 24 hours (AUC[0-24]) of DTG was assessed by a population PK modeling approach using pooled DTG PK data from multiple studies. For this study, blood samples for pharmacokinetic assessments were collected pre-dose on Day 8 and at Weeks 4 and 24, at 1-3 hours post-dose on Day 8, and at 1-3 hours or 4-12 hours post-dose at Weeks 4 and 24. The Pharmacokinetic (PK) Concentration Population used is defined as all subjects who received DTG, had undergone PK sampling during the study, and provided evaluable DTG plasma concentration data.

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

End point timeframe:

Day 8, Week 4, and Week 24

| | | | | |
|--|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 183 ^[23] | | | |
| Units: µg*hour/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| AUC(0-tau) | 36.7 (35 to 38.6) | | | |
| AUC(0-24) | 73.5 (70 to 77.1) | | | |

Notes:

[23] - The Pharmacokinetic (PK) Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: C0 assessment of DTG

| | |
|-----------------|----------------------|
| End point title | C0 assessment of DTG |
|-----------------|----------------------|

End point description:

The plasma DTG concentration immediately prior to dosing at steady state (C0) was assessed at Day 8, Week 4, and Week 24. Blood samples for pharmacokinetic assessments were collected pre-dose and 1-3 hours post-dose on Day 8 and at Week 4 and 4-12 hours post-dose at Week 24. Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the Pharmacokinetic Parameter Population. The Pharmacokinetic (PK) Concentration Population used is defined as all subjects who received DTG, had undergone PK sampling during the study, and provided evaluable DTG plasma concentration data.

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

End point timeframe:

Day 8, Week 4, and Week 24

| | | | | |
|---|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 161 ^[24] | | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 8, n=148 | 2.36 (± 91) | | | |
| Week 4, n=161 | 1.9 (± 113) | | | |
| Week 24, n=135 | 2.14 (± 93) | | | |

Notes:

[24] - Pharmacokinetic (PK) Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated treatment-emergent integrase (IN) mutations detected at the time of protocol-defined virologic failure (PDVF) as a measure of genotypic resistance

| | |
|-----------------|--|
| End point title | Number of participants with the indicated treatment-emergent integrase (IN) mutations detected at the time of protocol-defined virologic failure (PDVF) as a measure of genotypic resistance |
|-----------------|--|

End point description:

Analysis of changes at specific amino acids in the IN coding region associated with resistance to raltegravir, elvitegravir, or DTG was performed at Day 1 and at the time of PDVF. PDVF is a $<0.5 \log_{10}$ c/mL decrease in plasma HIV-1 RNA at Day 8 unless the absolute value is <400 c/mL. PDVF after Day 8 is defined as virological non-responses (decrease in plasma HIV-1 RNA of $<1 \log_{10}$ c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA <400 c/mL and confirmed plasma HIV-1 RNA levels ≥ 400 c/mL on or after Week 24) & virological rebound (confirmed rebound in plasma HIV-1 RNA levels to ≥ 400 c/mL after prior confirmed suppression to <400 c/mL & confirmed plasma HIV-1 RNA levels $>1 \log_{10}$ c/mL above the nadir value [nadir: ≥ 400 c/mL]). PDVF Genotypic Resistance (GR) populations: all par. in the ITT-E Population with available on-treatment GR data at the time of PDVF. Only par. with baseline IN mutations with PDVF who had paired baseline and time of PDVF samples considered.

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

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

| End point values | Dolutegravir 50 mg BID | | | |
|-----------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 ^[25] | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Any IN mutation | 25 | | | |
| T97A | 8 | | | |
| T97T/A | 4 | | | |
| E138A | 1 | | | |
| E138E/A | 1 | | | |
| E138E/K | 3 | | | |
| E138K | 4 | | | |
| E138T/A | 1 | | | |
| N155H | 6 | | | |
| N155N/H | 1 | | | |
| Q148H | 3 | | | |
| Q148Q/H | 2 | | | |
| Q148R | 1 | | | |
| Q148Q/R/K | 1 | | | |
| G140G/S | 1 | | | |
| G140S | 3 | | | |
| L74L/M/V | 1 | | | |
| L74L/M | 1 | | | |
| L74I | 1 | | | |
| E92E/Q | 2 | | | |
| S147G | 2 | | | |
| E157E/Q | 1 | | | |
| V151V/M/I | 1 | | | |
| Y143Y/H | 1 | | | |

Notes:

[25] - PDVF Genotypic Resistance Populations

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated fold increase in DTG FC (fold change in IC50 [50% inhibitory concentration] relative to wild-type virus) between Baseline and the time of PDVF, as a measure of post-Baseline phenotypic resistance

| | |
|-----------------|---|
| End point title | Number of participants with the indicated fold increase in DTG FC (fold change in IC50 [50% inhibitory concentration] relative to wild-type virus) between Baseline and the time of PDVF, as a measure of post-Baseline phenotypic resistance |
|-----------------|---|

End point description:

The FC in IC50 for DTG relative to wild-type virus was determined for virus isolated at Baseline & at the time of PDVF. The number of participants with the indicated change (ratio) in the two values at the time of PDVF is presented. PDVF is defined as a <0.5 log10 c/mL decrease in plasma HIV-1 RNA at Day 8 unless the absolute value is <400 c/mL. PDVF after Day 8 was defined for virological non-response (decrease in plasma HIV-1 RNA of less than 1 log10 c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA <400 c/mL and confirmed plasma HIV-1 RNA levels \geq 400 c/mL on or after Week 24) & virological rebound (confirmed rebound in plasma HIV-1 RNA levels to \geq 400 c/mL after prior confirmed suppression to <400 c/mL and confirmed plasma HIV-1 RNA levels >1 log10 c/mL above the nadir value, where nadir is \geq 400 c/mL). PDVF Phenotypic Resistance Populations are the only par. with Baseline DTG IC50 with PDVF who had paired Baseline & time of virological failure are considered.

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

End point timeframe:

From the day of the first dose of study drug until end of treatment visit for each participant, up to Week 180 (median of 758 days)

| | | | | |
|-----------------------------|------------------------|--|--|--|
| End point values | Dolutegravir 50 mg BID | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 ^[26] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| <1 fold | 6 | | | |
| 1-<2 fold | 16 | | | |
| 2-<4 fold | 4 | | | |
| 4-<8 fold | 4 | | | |
| \geq 8 fold | 12 | | | |
| Missing | 3 | | | |

Notes:

[26] - PDVF Phenotypic Resistance Populations.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from start of study treatment until the end of treatment visit for each participant (up to Week 180)

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were reported for the Safety population consisted of all participants who received at least one dose of investigational product.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Dolutegravir 50 mg BID |
|-----------------------|------------------------|

Reporting group description:

Participants received DTG 50 mg BID.

| Serious adverse events | Dolutegravir 50 mg BID | | |
|---|------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 46 / 183 (25.14%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anogenital warts | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bile duct cancer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hodgkin's disease recurrent | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal cancer stage I | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hodgkin's disease | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lip and/or oral cavity cancer stage 0 | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of the cervix | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertensive emergency | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Immune reconstitution inflammatory syndrome | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian mass | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung disorder | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopneumopathy | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nerve compression | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Parotid gland enlargement | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 183 (1.09%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nodular regenerative hyperplasia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint destruction | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|--|-----------------------------------|--|--|--|
| Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 5 / 183 (2.73%) 0 / 5 0 / 1 | | | |
| Progressive multifocal leukoencephalopathy subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 183 (1.09%) 0 / 2 0 / 1 | | | |
| Cytomegalovirus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 183 (0.55%) 0 / 1 0 / 0 | | | |
| Cytomegalovirus viraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 183 (0.55%) 0 / 1 0 / 0 | | | |
| Gastroenteritis viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 183 (0.55%) 0 / 1 0 / 0 | | | |
| Epstein-Barr virus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 183 (0.55%) 0 / 1 0 / 0 | | | |
| Herpes ophthalmic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 183 (0.55%) 0 / 1 0 / 0 | | | |
| Herpes zoster subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 183 (0.55%) 0 / 1 0 / 0 | | | |

| | | | | |
|---|-----------------|--|--|--|
| Lung infection | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal candidiasis | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumococcal sepsis | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Streptococcal sepsis | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Eye infection toxoplasmal | | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes virus infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orchitis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Dolutegravir 50 mg BID | | |
|---|---------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 143 / 183 (78.14%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | | |
| occurrences (all) | 11 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 24 / 183 (13.11%) | | |
| occurrences (all) | 27 | | |
| General disorders and administration | | | |

| | | | |
|---|-------------------|--|--|
| site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 17 / 183 (9.29%) | | |
| occurrences (all) | 17 | | |
| Pyrexia | | | |
| subjects affected / exposed | 19 / 183 (10.38%) | | |
| occurrences (all) | 25 | | |
| Asthenia | | | |
| subjects affected / exposed | 13 / 183 (7.10%) | | |
| occurrences (all) | 17 | | |
| Injection site reaction | | | |
| subjects affected / exposed | 12 / 183 (6.56%) | | |
| occurrences (all) | 12 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 41 / 183 (22.40%) | | |
| occurrences (all) | 53 | | |
| Nausea | | | |
| subjects affected / exposed | 26 / 183 (14.21%) | | |
| occurrences (all) | 29 | | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 183 (7.10%) | | |
| occurrences (all) | 13 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | | |
| occurrences (all) | 14 | | |
| Constipation | | | |
| subjects affected / exposed | 12 / 183 (6.56%) | | |
| occurrences (all) | 14 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 29 / 183 (15.85%) | | |
| occurrences (all) | 36 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 10 / 183 (5.46%) | | |
| occurrences (all) | 10 | | |

| | | | |
|--|--|--|--|
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>17 / 183 (9.29%)</p> <p>19</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>11 / 183 (6.01%)</p> <p>14</p> | | | |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>14 / 183 (7.65%)</p> <p>15</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>10 / 183 (5.46%)</p> <p>11</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>18 / 183 (9.84%)</p> <p>22</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>12 / 183 (6.56%)</p> <p>17</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>11 / 183 (6.01%)</p> <p>13</p> | | | |
| <p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>25 / 183 (13.66%)</p> <p>35</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>22 / 183 (12.02%)</p> <p>25</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>12 / 183 (6.56%)</p> <p>14</p> <p>Rhinitis</p> | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 11 / 183 (6.01%) | | |
| occurrences (all) | 14 | | |
| Influenza | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | | |
| occurrences (all) | 11 | | |
| Sinusitis | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | | |
| occurrences (all) | 13 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 07 September 2011 | Clarification of statistical algorithm (MSDF), guidance on Entecavir use provided, cautionary text added to Permitted Medications and Non-Drug Therapies section, Rifapentine added to Prohibited Medications plus additional guidance, management of subjects with Decline in Renal Function amended, addition of section on Rash management, addition of ATV use to exceptions statement in Appendix 3: Child-Pugh classification, correction of typographical errors and minor edits. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported