Clinical trial results:
A Phase IIb pilot study to assess the antiviral activity of GSK1349572 containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance

Summary

EudraCT number	2009-010270-37
Trial protocol	FR ES IT
Global end of trial date	23 January 2015

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	13 August 2015

Trial information

Trial identification

Sponsor protocol code	ING112961

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, 1 866-435-7343,
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	18 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the short-term antiviral activity of GSK1349572 + failing background regimen.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2009
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	Spain: 5
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	51
EEA total number of subjects	32

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)	50
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants (par.) recruited initially to Cohort I and subsequently to Cohort II. Recruitment to Cohort I was closed 9 months before recruitment to Cohort II was opened. Recruitment was not randomized.

Pre-assignment

Screening details:

The study will included ART-experienced participants with either current or past virologic failure to raltegravir.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort I (DTG 50 mg OD)

Arm description:

Participants received dolutegravir (DTG) 50 milligrams (mg) once a day (OD).

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 once daily (Cohort I)

Arm title	Cohort II (DTG 50 mg BID)

Arm description:

Participants received DTG 50 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:

50 mg twice daily (Cohort II)

Number of subjects in period 1	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)
Started	27	24
Completed	11	14
Not completed	16	10
Adverse event, serious fatal	3	2
Insufficient Viral Load Response	12	3
Adverse event, non-fatal	-	1
Lost to follow-up	-	3
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort I (DTG 50 mg OD)
Reporting group description:	
Participants received dolutegravir (DTG) 50 milligrams (mg) once a day (OD).	
Reporting group title	Cohort II (DTG 50 mg BID)
Reporting group description:	
Participants received DTG 50 mg twice a day (BID).	

Reporting group values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)	Total
Number of subjects	27	24	51
Age categorical Units: Subjects			
Age continuous Units: years			
median	48	47	
full range (min-max)	19 to 61	33 to 68	-
Gender categorical Units: Subjects			
Female	2	6	8
Male	25	18	43
Race Units: Subjects			
African American/African Heritage	3	5	8
White-Arabic/North African Heritage	1	1	2
White-White/Caucasian/European Heritage	23	18	41

End points

End points reporting groups

Reporting group title	Cohort I (DTG 50 mg OD)
Reporting group description:	
Participants received dolutegravir (DTG) 50 milligrams (mg) once a day (OD).	
Reporting group title	Cohort II (DTG 50 mg BID)
Reporting group description:	
Participants received DTG 50 mg twice a day (BID).	

Primary: Number of participants who achieved HIV-1 RNA <400 copies (c)/milliliter (mL) or at least 0.7 log10 c/mL below their Baseline value at Day 11

End point title	Number of participants who achieved HIV-1 RNA <400 copies (c)/milliliter (mL) or at least 0.7 log10 c/mL below their Baseline value at Day 11[1]

End point description:

The number of participants who achieved Plasma Human Immunodeficiency Virus-1 (HIV-1) Ribonucleic Acid (RNA) <400 c/mL or at least 0.7 log10 c/mL below their Baseline value at Day 11 was assessed. The last observation was carried forward if a participant had missed the Day 11 visit. The Baseline observation was carried forward if a participant had discontinued the treatment before Day 11. Blood samples for assessment of HIV-1 RNA levels were collected at Baseline and Day 11. Intent-to-Treat Exposed (ITT-E) Population: all participants who received at least one dose of study medication and who had at least one post-Baseline measure of plasma HIV-1 RNA.

End point type	Primary

End point timeframe:

Baseline (Day 1) and Day 11

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: Statistical information is not permitted to be entered into the system for a single arm.

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[2]	24[3]		
Units: Participants	21	23		

Notes:

[2] - ITT-E Population

[3] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Plasma HIV-1 RNA at Day 6 to 8, Day 11, Weeks 4, 12, 24, 48, 72, 96, from Week 108 every 12 weeks up to study completion

End point title	Mean change from Baseline in Plasma HIV-1 RNA at Day 6 to 8, Day 11, Weeks 4, 12, 24, 48, 72, 96, from Week 108 every 12 weeks up to study completion

End point description:

Mean change from Baseline in Plasma HIV-1 RNA was assessed on Day 6 to 8, Day 11, and Weeks 4, 12, 24, 48, 72, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, and 264 using data of the observed cases. Study Day 1 was considered as Baseline. Change from Baseline was

calculated as the post-Baseline value minus the Baseline value. Only those participants available at the indicated time points were analyzed (represented by n=X, X in the category titles). 99999 represents NA.

End point type	Secondary

End point timeframe:

Baseline; Day 6 to 8; Day 11; Weeks 4, 12, 24, 48, 72, 96, from 108 every 12 weeks up to study completion

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[4]	24[5]		
Units: Log10 copies/mL				
arithmetic mean (standard deviation)				
Day 6 to 8, n=27, 24	-1.31 (± 0.71)	-1.4 (± 0.43)		
Day 11, n= 27, 24	-1.45 (± 0.77)	-1.76 (± 0.53)		
Week 4, n= 26, 24	-1.82 (± 1.03)	-2.06 (± 0.78)		
Week 12, n= 22, 24	-1.94 (± 1.14)	-2.3 (± 0.93)		
Week 24, n= 18, 22	-1.99 (± 1.08)	-2.5 (± 0.81)		
Week 48, n= 15, 20	-2.02 (± 1.07)	-2.63 (± 0.78)		
Week 72, n= 14, 18	-2.1 (± 1.03)	-2.71 (± 0.82)		
Week 96, n= 13, 15	-2.06 (± 1.13)	-2.58 (± 0.77)		
Week 108, n= 13, 17	-1.95 (± 1.2)	-2.69 (± 0.82)		
Week 120, n= 11, 17	-2.09 (± 1.15)	-2.67 (± 0.85)		
Week 132, n= 11, 17	-1.83 (± 1.01)	-2.66 (± 0.86)		
Week 144, n= 12, 15	-2.08 (± 1.29)	-2.62 (± 0.94)		
Week 156, n= 12, 15	-2.04 (± 1.36)	-2.65 (± 0.77)		
Week 168, n= 11, 14	-1.77 (± 1.26)	-2.72 (± 0.89)		
Week 180, n= 11, 10	-1.76 (± 1.11)	-2.56 (± 0.82)		
Week 192, n= 9, 7	-1.87 (± 1.16)	-2.51 (± 0.98)		
Week 204, n= 10, 6	-1.76 (± 1.21)	-2.35 (± 0.71)		
Week 216, n= 9, 6	-1.61 (± 1.08)	-2.35 (± 0.71)		
Week 228, n= 6, 4	-1.79 (± 1.08)	-2.33 (± 0.9)		
Week 240, n= 7, 0	-1.63 (± 1.13)	99999 (± 99999)		
Week 252, n= 4, 0	-1.72 (± 1.07)	99999 (± 99999)		
Week 264, n= 1, 0	-2.9 (± 99999)	99999 (± 99999)		

Notes:

[4] - ITT-E Population

[5] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved plasma HIV-1 RNA <400 c/mL and <50 c/mL at Baseline and Weeks 4, 12, 24, 48, 72, and 96: TLOVR analysis.

End point title	Number of participants who achieved plasma HIV-1 RNA <400 c/mL and <50 c/mL at Baseline and Weeks 4, 12, 24, 48, 72, and 96: TLOVR analysis.

End point description:

The number of participants with plasma HIV-1 RNA <400 c/mL or <50 c/mL was assessed at Weeks 4, 12, 24, 48, 72, and 96 per the Food and Drug Administration's Time to Loss of Virological Response (TLOVR) algorithm. Using the TLOVR algorithm, participants are considered to have failed on therapy if they never achieved confirmed RNA levels below the threshold, if they had confirmed rebound of RNA above the threshold, if they made a non-permitted change in background regimen, or if they permanently discontinued investigational product for any reason. 99999 represents NA.

End point type	Secondary

End point timeframe:

Baseline; Weeks 4, 12, 24, 48, 72, and 96

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[6]	24[7]		
Units: Participants				
Baseline, <50 c/mL	0	0		
Week 4, <50 c/mL	9	12		
Week 12, <50 c/mL	13	16		
Week 24, <50 c/mL	11	19		
Week 48, <50 c/mL	9	17		
Week 72, <50 c/mL	8	99999		
Week 96, <50 c/mL	7	99999		
Baseline, <400 c/mL	0	0		
Week 4, <400 c/mL	16	17		
Week 12, <400 c/mL	16	20		
Week 24, <400 c/mL	14	20		
Week 48, <400 c/mL	13	18		
Week 72, <400 c/mL	12	99999		
Week 96, <400 c/mL	10	99999		

Notes:

[6] - ITT-E Population

[7] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants who achieved plasma HIV-1 RNA <400 c/mL and <50 c/mL from Week 48 every 12 weeks up to study completion

End point title	Proportion of participants who achieved plasma HIV-1 RNA <400 c/mL and <50 c/mL from Week 48 every 12 weeks up to study completion

End point description:

The number of participants with plasma HIV-1 RNA <400 c/mL or <50 c/mL was assessed at Weeks 48, 72, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, and 264 using data of observed cases. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). 99999 represents NA.

End point type	Secondary

End point timeframe:

From Week 48 every 12 weeks up to study completion

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[8]	24[9]		
Units: Percentage of Participants				
Week 48, <50 c/mL, n=15, 20	60	80		
Week 60, <50 c/mL, n=13, 18	69	94		
Week 72, <50 c/mL, n=14, 18	64	78		
Week 84, <50 c/mL, n=14, 18	57	78		
Week 96, <50 c/mL, n=13, 15	54	87		
Week 108, <50 c/mL, n=13, 17	54	88		
Week 120, <50 c/mL, n=11, 17	55	88		
Week 132, <50 c/mL, n=11, 17	55	82		
Week 144, <50 c/mL, n=12, 15	58	87		
Week 156, <50 c/mL, n=12, 15	67	93		
Week 168, <50 c/mL, n=11, 14	64	86		
Week 180, <50 c/mL, n=11, 10	64	100		
Week 192, <50 c/mL, n= 9, 7	67	100		
Week 204, <50 c/mL, n= 10, 6	50	100		
Week 216, <50 c/mL, n= 9, 6	56	100		
Week 228, <50 c/mL, n=6, 4	67	100		
Week 240, <50 c/mL, n=7,0	57	99999		
Week 252, <50 c/mL, n=4, 0	50	99999		
Week 264, <50 c/mL, n=1, 0	100	99999		
Week 48, <400 c/mL, n=15, 20	73	95		
Week 60,<400 c/mL, n=13, 18	92	100		
Week 72,<400 c/mL, n=14, 18	79	100		
Week 84,<400 c/mL, n=14, 18	71	94		
Week 96,<400 c/mL, n=13, 15	85	100		
Week 108, <400 c/mL, n=13,17	85	100		
Week 120,<400 c/mL, n=11, 17	82	94		
Week 132,<400 c/mL, n=11,17	82	94		
Week 144,<400 c/mL, n=12, 15	83	93		
Week 156,<400 c/mL, n=12, 15	75	100		
Week 168,<400 c/mL, n=11, 14	82	100		
Week 180,<400 c/mL, n=11, 10	73	100		
Week 192,<400 c/mL, n=9, 7	78	100		
Week 204,<400 c/mL, n=10, 6	70	100		
Week 216,<400 c/mL, n=9, 6	56	100		
Week 228, <400 c/mL, n=6, 4	67	100		
Week 240, <400 c/mL, n=7, 0	71	99999		
Week 252, <400 c/mL, n=4, 0	50	99999		
Week 264, <400 c/mL, n=1, 0	100	99999		

Notes:

[8] - ITT-E Population

[9] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CD4+ cell count at Day 11 and Weeks 4, 12, 24, 48, 72, 96, Week 108 every 12 weeks up to study completion

End point title	Change from baseline in CD4+ cell count at Day 11 and Weeks 4, 12, 24, 48, 72, 96, Week 108 every 12 weeks up to study completion

End point description:

Change from Baseline in CD4+ cell count was assessed at Day 11 and at Weeks 4, 12, 24, 48, 72, 96,108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, and 264. Study Day 1 was considered as Baseline.Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants available at the indicated time points were analyzed (represented by n=X, X in the category titles). 99999 represents NA.

End point type	Secondary

End point timeframe:

Baseline; Day 11; Weeks 4, 12, 24, 48, 72, 96, from 108 every 12 weeks up to study completion

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[10]	24[11]		
Units: cells per cubic millimeter (mm^3)				
median (inter-quartile range (Q1-Q3))				
Baseline, n=27, 24	114 (44 to 227)	202 (19 to 384)		
Day 11, n=27, 24	34 (2 to 71)	14 (0 to 69)		
Week 4, n=27, 24	57 (33 to 108)	35 (8 to 69)		
Week 12, n= 22, 24	84 (26 to 124)	57 (8 to 103)		
Week 24, n=17, 22	78 (54 to 175)	79 (17 to 147)		
Week 48, n=15, 20	102 (29 to 160)	106 (45 to 245)		
Week 72, n=14, 18	163 (58 to 204)	191.5 (80 to 277)		
Week 96, n=13, 15	142 (75 to 202)	189 (75 to 280)		
Week 108, n=13, 17	124 (68 to 249)	155 (91 to 276)		
Week 120, n=11, 17	221 (62 to 306)	221 (135 to 314)		
Week 132, n=11, 17	97 (26 to 303)	158 (129 to 384)		
Week 144, n=12, 15	121 (28 to 284)	278 (113 to 340)		
Week 156, n=12, 15	212 (64 to 378)	223 (131 to 309)		
Week 168, n=11, 13	97 (-102 to 365)	271 (93 to 357)		
Week 180, n=11, 10	125 (55 to 327)	224 (163 to 288)		
Week 192, n=10, 7	94 (61 to 291)	343 (304 to 429)		
Week 204, n=10, 6	92 (47 to 364)	264 (186 to 370)		
Week 216, n=9, 6	172 (48 to 416)	252 (147 to 421)		

Week 228, n=7, 3	148 (66 to 357)	417 (-12 to 633)		
Week 240, n=7, 0	158 (119 to 470)	99999 (99999 to 99999)		
Week 252, n=4, 0	157 (109 to 282)	99999 (99999 to 99999)		
Week 264, n=1, 0	560 (560 to 560)	99999 (99999 to 99999)		

Notes:

[10] - ITT-E Population

[11] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax, Cmin, and Ctau of DTG

End point title	Cmax, Cmin, and Ctau of DTG

End point description:

The maximum plasma concentration (Cmax), minimum plasma concentration (Cmin), and concentration at the end of a dosing interval (Ctau) of DTG were assessed at Day 10. Blood samples for pharmacokinetic (PK) assessments were collected at pre-dose (within 15 minutes prior to dose) and 2, 3, 4, 8, and 24 hours post-dose on Day 10 for DTG 50 mg OD and pre-dose (within 15 minutes prior to dose) and 2, 3, 4 and 8 hours post morning dose and 12 hours post evening dose for DTG 50 mg BID. Pharmacokinetic (PK) Parameter Population: all participants who provided at least one evaluable PK concentration.

End point type	Secondary

End point timeframe:

Day 10

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[12]	23[13]		
Units: Micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cmax	3.04 (± 38)	5.41 (± 40)		
Ctau	0.69 (± 91)	2.72 (± 70)		
Cmin	0.48 (± 136)	2.61 (± 67)		

Notes:

[12] - PK Parameter Population

[13] - PK Parameter 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 10, and Weeks 4 and 24. Blood samples for pharmacokinetic assessments were collected at pre-dose (within

15 minutes prior to dose).

End point type	Secondary

End point timeframe:

Day 10; Weeks 4 and 24

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[14]	23[15]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
C0, Day 10	0.51 (± 139)	3.2 (± 69)		
C0, Week 4	0.57 (± 100)	2.55 (± 63)		
C0, Week 24	0.38 (± 114)	2.38 (± 69)		

Notes:

[14] - PK Parameter Population

[15] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of DTG

End point title	Tmax of DTG

End point description:

The tmax is defined as the time of occurrence of the maximum plasma concentration (Cmax). The tmax was assessed at Day 10. Blood samples for pharmacokinetic assessments were collected at pre-dose (within 15 minutes prior to dose) and 2, 3, 4, 8, and 24 hours post-dose on Day 10 for DTG 50 mg OD and pre-dose (within 15 minutes prior to dose) and 2, 3, 4 and 8 hours post morning dose and 12 hours post evening dose for DTG 50 mg BID.

End point type	Secondary

End point timeframe:

Day 10

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[16]	23[17]		
Units: Hours				
median (full range (min-max))	2.97 (1.97 to 7.92)	2 (0 to 7.87)		

Notes:

[16] - PK Parameter Population

[17] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24 assessment of DTG

End point title	AUC0-24 assessment of DTG

End point description:

AUC is defined as the area under the DTG concentration-time curve as a measure of drug exposure. AUC(0-24) is defined as the area under the concentration-time curve from time zero (pre-dose) to 24 hours. AUC0-24 of DTG was assessed at Day 10. Blood samples for pharmacokinetic assessments were collected at pre-dose (within 15 minutes prior to dose) and 2, 3, 4, 8, and 24 hours post-dose on Day 10 for DTG 50 mg OD and pre-dose (within 15 minutes prior to dose) and 2, 3, 4 and 8 hours post morning dose and 12 hours post evening dose for DTG 50 mg BID.

End point type	Secondary

End point timeframe:

Day 10

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[18]	23[19]		
Units: Micrograms*hour per milliliter (µg*hr/mL				
geometric mean (geometric coefficient of variation)	36.46 (± 53)	93.36 (± 50)		

Notes:

[18] - PK Parameter Population

[19] - PK Parameter Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated HIV-1 associated conditions, excluding recurrences

End point title	Number of participants with the indicated HIV-1 associated conditions, excluding recurrences

End point description:

The number of par. with post-Baseline emergent HIV-1 disease progression (Acquired immunodeficiency syndrome (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 (par. with asymptomatic HIV infection, acute HIV infection with accompanying illness, or persistent generalized lymphadenopathy), Category B (par. 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). Par. may have more than one HIV associated condition. condition is counted only once

End point type	Secondary

End point timeframe:

From the day of the first dose of study drug until study completion (median 605 days for Cohort I, median 1181 days for Cohort II)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[20]	24[21]		
Units: Participants				
Category B, Candidiasis, oropharyngeal	3	2		
Category B, Hairy leukoplakia, oral	2	0		
Category B, Herpes Zoster	2	0		
Category C, Herpes simplex	1	0		
Category C, Candidiasis, esophageal	0	1		
Category C, Cytomegalovirus retinitis	0	1		
Category C, Kaposi's sarcoma	1	0		
Category C, Lymphoma, Burkitt's	0	1		
Category C, Lymphoma, immunoblastic	1	0		
Death, Brain mass	1	0		
Death, Completed suicide	0	1		
Death, Febrile bone marrow aplasia	1	0		
Death, Immunoblastic lymphoma	1	0		
Death, Acute pulmonary oedema	1	0		
Death, Anaemia	0	1		
Death, Haemochromatosis	0	1		
Death, Hepatic fibrosis	0	1		
Other: Cryptosporidiosis, acute intestinal	0	1		
Other: leukoplasia of both side of the tongue	1	0		

Notes:

[20] - ITT-E Population. Each condition is counted only once per participant regardless of recurrence.

[21] - ITT-E Population. Each condition is counted only once per participant regardless of recurrence.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with HIV-1 associated disease progression with the indicated shifts to CDC Class C or death

End point title	Number of participants with HIV-1 associated disease progression with the indicated shifts to CDC Class C or death

End point description:

The number of participants with HIV-1 disease progression (AIDS or death) was assessed per the 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 study completion (median 605 days for Cohort I, median 1181 days for Cohort II)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[22]	24[23]		
Units: Participants				
From CDC class A to CDC class C	0	2		
From CDC class B to CDC class C	0	2		
From CDC class C to new CDC class C	1	0		
From CDC Class A, B, or C to death	3	2		

Notes:

[22] - ITT-E Population

[23] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants (cumulative) with protocol-defined virological failure (PDVF) at Day 11 and Weeks 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, Week 108 every 12 weeks up to study completion

End point title	Number of participants (cumulative) with protocol-defined virological failure (PDVF) at Day 11 and Weeks 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, Week 108 every 12 weeks up to study completion

End point description:

PDVF is defined in relation to Baseline plasma HIV-1 RNA levels: at Day 11, a decrease of <0.7 log10 c/mL unless <400 c/mL; at Weeks 8 to <16, a decrease of <1.0 log10 c/mL unless <400 c/mL or an increase of >= 1.0 log10 c/mL from nadir; and at or after Week 16, ≥400 c/mL. PDVF at Day 11 was based on a single plasma HIV-1 RNA evaluation and did not require confirmation. Confirmation testing was required for visits at or after Week 8. For the combination treatment phase, all HIV-1 RNA samples that meet a criterion for suspected PDVF must be confirmed by a second measurement performed at least 1 week but not more than 4 weeks apart from the date of the original sample. 99999 represents NA.

End point type	Secondary

End point timeframe:

Day 11; Weeks 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, from Week 108 every 12 weeks up to study completion

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[24]	24[25]		
Units: Participants				
Day 11	6	1		
Week 8	7	3		
Week 12	9	3		
Week 16	10	5		
Week 20	10	5		
Week 24	12	5		
Week 32	12	5		
Week 40	12	5		
Week 48	13	5		
Week 60	13	5		

Week 72	14	6		
Week 84	15	6		
Week 96	16	6		
Week 108	16	6		
Week 120	16	6		
Week 132	16	6		
Week 144	16	7		
Week 156	16	7		
Week 168	16	7		
Week 180	16	7		
Week 192	16	7		
Week 204	16	7		
Week 216	17	7		
Week 228	18	7		
Week 240	18	99999		
Week 252	18	99999		
Week 264	18	99999		

Notes:

[24] - ITT-E Population

[25] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated genotypic resistance at Baseline

End point title	Number of participants with the indicated genotypic resistance at Baseline

End point description:

At Baseline, the integrase genotypic results were used to document resistance to raltegravir (RAL) and for the allocation of participants to one of two genotypic groups according to their RAL signature mutations to ensure a broad range of sensitivity to DTG. These results were not used to pre-define subgroup for analysis.

End point type	Secondary

End point timeframe:

Baseline

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[26]	24[27]		
Units: Participants				
Q148 + 2	3	2		
Q 148 + 1	4	8		
Mixture	2	1		
Y143	12	6		
N155	4	6		
Other	2	1		

Notes:

[26] - ITT-E Population

[27] - ITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median Fold change in sensitivity to DTG by the Baseline (Day 1) IN mutational group

End point title	Median Fold change in sensitivity to DTG by the Baseline (Day 1) IN mutational group

End point description:

Summary of median fold change in sensitivity to DTG by Integrase (IN) mutational group was assessed. The IN mutational group comprises of the following mutations: Q148 +2, Q148 +1, mixture (participants with virus containing more than one Y143, Q148 or N155 mutation at Day 1), Y143, N155, other (participants with virus having no mutations at codons 143, 148, or 155 at Day 1). Fold change (FC) is the fold change in 50% Inhibitory Concentration (IC50) relative to the wild-type control virus.

End point type	Secondary

End point timeframe:

Baseline (Day 1)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[28]	24[29]		
Units: Percentage				
median (full range (min-max))				
Q148 + 2, n=3, 2	21 (14 to 35)	4 (2.1 to 6)		
Q148 + 1, n=4, 8	5.5 (3.3 to 25)	5.5 (4.1 to 8.2)		
Mixture, n=2, 1	7.8 (6.5 to 9.1)	9.48 (9.48 to 9.48)		
Y143, n=12, 6	1.1 (0.6 to 1.4)	1.2 (0.92 to 1.8)		
N155, n=4, 6	1.8 (1.5 to 5.1)	2.3 (1.3 to 4)		
Other, n=2, 1	1.2 (0.9 to 1.5)	0.87 (0.87 to 0.87)		

Notes:

[28] - ITT-E Population

[29] - ITT-E 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:

An 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 defined in relation to Baseline plasma HIV-1 RNA levels: at Day 11, a decrease of <0.7 log10 c/mL unless <400 c/mL; at Weeks 8 to <16, a decrease of <1.0 log10 c/mL unless <400 c/mL or an increase of >= 1.0 log10 c/mL from nadir; and at or after Week 16, ≥400 c/mL. PDVF at Day 11 was based on a single plasma HIV-1 RNA evaluation and did not require confirmation. Confirmation testing was required for visits at or after Week 8. For the combination treatment phase, all HIV-1 RNA samples that meet a criterion for suspected PDVF must be confirmed by a second measurement performed at least 1 week but not more than 4 weeks apart from the date of the original sample. On-treatment Genotypic Resistance Population: all ITT-E participants who met the criteria for protocol-defined virological failure (PDVF).

End point type	Secondary

End point timeframe:

From Baseline (Day 1) until study completion (median 605 days for Cohort I, median 1181 days for Cohort II)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[30]	7[31]		
Units: Participants				
Any	11	5		
E138T	0	1		
N155H	3	4		
T97A	2	0		
E92E/Q	0	1		
G140S	3	0		
L74I/M	1	0		
Q148H	2	0		
E138E/A	1	0		
E138E/K	1	2		
L74I/M/I	1	0		
L74M	1	0		
L74I	1	0		
T97T/A	0	2		
Q148R	1	0		
S147G	3	0		
E92E/V	0	1		
L68L/I	1	0		

Notes:

[30] - On-treatment Genotypic Resistance Population

[31] - On-treatment Genotypic Resistance Population

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 relative to wild-type virus) between Baseline (BL) 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 relative to wild-type virus) between Baseline (BL) and the time of PDVF, as a measure of post-Baseline phenotypic resistance

End point description:

FC in IC50 (50% inhibitory concentration) for DTG relative to wild-type virus was determined for virus isolated at BL and PDVF. Number of par. with the indicated change (ratio) in the two values at the time of PDVF is presented. PDVF is defined in relation to Baseline plasma HIV-1 RNA levels: at Day 11, a decrease of <0.7 log10 c/mL unless <400 c/mL; at Weeks 8 to <16, a decrease of <1.0 log10 c/mL unless <400 c/mL or an increase of >= 1.0 log10 c/mL from nadir; and at or after Week 16, ≥400 c/mL. PDVF at Day 11 was based on a single plasma HIV-1 RNA evaluation and did not require confirmation. Confirmation testing was required for visits at or after Week 8. For the combination treatment phase, all HIV-1 RNA samples that meet a criterion for suspected PDVF must be confirmed by a second measurement performed at least 1 week but not more than 4 weeks apart from the date of the original sample. Only par. with both BL and PDVF time-point DTG phenotypic data were considered for analysis.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) until study completion (median 605 days for Cohort I, median 1181 days for Cohort II)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[32]	7[33]		
Units: Participants				
<1 fold	3	0		
1-<2 fold	4	2		
2-<4 fold	1	0		
4-<8 fold	1	2		
>=8 fold	8	3		

Notes:

[32] - PDVF Phenotypic Resistance Population:all ITT-E par. with phenotypic resistance data at PDVF failure

[33] - PDVF Phenotypic Resistance Population:all ITT-E par. with phenotypic resistance data at PDVF failure

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Grade 3 and Grade 4 clinical chemistry toxicities

End point title	Number of participants with the indicated Grade 3 and Grade 4 clinical chemistry toxicities

End point description:

Hematology and clinical chemistry data were summarized according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004. Grade 1, Mild; Grade 2, Moderate; Grade 3, Severe; Grade 4, Potentially life-threatening. Data are presented for only those parameters for which an increase to Grade 3 or Grade 4 occurred. The Grade 3 and Grade 4 clinical chemistry toxicities included: Albumin, Alkaline Phosphatase, Amylase, Aspartate Amino Transferase, Carbon dioxide content/Bicarbonate, Creatinine, Creatinine Clearance, Hypercalcemia, Hyperglycaemia, Hyperkalemia, Hypernatremia, Hypocalcemia, Hypoglycaemia, Hypokalemia, Hyponatremia, LDL Cholesterol, Magnesium, Phosphorus inorganic, aTotal Bilirubin, Alanine Amino Transferase, Calcium, Chloride, Cholesterol, Creatine Kinase, Direct Bilirubin, Glucose, High Density Lipid (HDL), Cholesterol direct, Lipase, Potassium, Sodium, Total Cholesterol, Triglycerides, Urea/Blood Urine Nitrogen.

End point type	Secondary

End point timeframe:

From the day of the first dose of study drug until study completion (median 605 days for Cohort I, median 1181 days for Cohort II)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[34]	24[35]		
Units: Participants				
Albumin, Grade 3	0	0		
Albumin, Grade 4	0	0		
Alkaline Phosphatase, Grade 3	0	0		
Alkaline Phosphatase, Grade 4	0	0		
Amylase, Grade 3	1	2		
Amylase, Grade 4	1	0		
Aspartate Amino Transferase, Grade 3	0	0		
Aspartate Amino Transferase, Grade 4	0	0		
Carbon dioxide content/Bicarbonate, Grade 3	0	0		
Carbon dioxide content/Bicarbonate, Grade 4	0	0		
Creatinine, Grade 3	0	0		
Creatinine, Grade 4	0	0		
Creatinine Clearance, estimated, Grade 3	0	0		
Creatinine Clearance, estimated, Grade 4	0	0		
Hypercalcemia, Grade 3	0	0		
Hypercalcemia, Grade 4	0	0		
Hyperglycaemia, Grade 3	0	0		
Hyperglycaemia, Grade 4	0	0		
Hyperkalemia, Grade 3	0	0		
Hyperkalemia, Grade 4	0	0		
Hypernatremia, Grade 3	1	0		
Hypernatremia, Grade 4	0	0		
Hypocalcemia, Grade 3	0	0		
Hypocalcemia, Grade 4	0	0		
Hypoglycaemia, Grade 3	1	0		
Hypoglycaemia, Grade 4	0	1		
Hypokalemia, Grade 3	0	0		
Hypokalemia, Grade 4	0	0		
Hyponatremia, Grade 3	0	0		
Hyponatremia, Grade 4	0	0		
LDL Cholesterol, Grade 3	2	1		
LDL Cholesterol, Grade 4	0	0		
Magnesium, Grade 3	0	0		
Magnesium, Grade 4	0	0		
Phosphorus inorganic, Grade 3	4	3		
Phosphorus inorganic, Grade 4	0	0		
Total Bilirubin, Grade 3	0	2		

Total Bilirubin, Grade 4	0	1		
Alanine Amino Transferase ,Grade 3	0	1		
Alanine Amino Transferase ,Grade 4	0	0		
Calcium,Grade 3	0	0		
Calcium,Grade 4	0	0		
Chloride,Grade 3	0	0		
Chloride,Grade 4	0	0		
Cholesterol,Grade 3	1	1		
Cholesterol,Grade 4	0	0		
Creatine Kinase,Grade 3	0	0		
Creatine Kinase,Grade 4	0	0		
Direct Bilirubin,Grade 3	0	0		
Direct Bilirubin,Grade 4	0	0		
Glucose,Grade 3	1	0		
Glucose,Grade 4	0	1		
HDL Cholesterol direct,Grade 3	0	0		
HDL Cholesterol direct,Grade 4	0	0		
Lipase,Grade 3	2	3		
Lipase,Grade 4	1	1		
Potassium,Grade 3	0	0		
Potassium,Grade 4	0	0		
Sodium,Grade 3	1	0		
Sodium,Grade 4	0	0		
Total Cholesterol/HDLratio, Grade 3	0	0		
Total Cholesterol/HDLratio, Grade 4	0	0		
Triglycerides,Grade 3	0	2		
Triglycerides,Grade 4	0	0		
Urea/BUN,Grade 3	0	0		
Urea/BUN,Grade 4	0	0		

Notes:

[34] - Safety Population: all participants that took at least one dose of DTG

[35] - Safety Population: all participants that took at least one dose of DTG

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Grade 3 and Grade 4 hematological toxicities

End point title	Number of participants with the indicated Grade 3 and Grade 4 hematological toxicities

End point description:

Hematology and clinical chemistry data were summarized according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004. Grade 1, Mild; Grade 2, Moderate; Grade 3, Severe; Grade 4, Potentially life-threatening. Data are presented for only those parameters for which an increase to Grade 3 or Grade 4 occurred. The Grade 3 and Grade 4 hematological toxicities included: Hemoglobin, Platelet Count, Total Neutrophils, and White Blood Cell count.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) until study completion (median 605 days for Cohort I, median 1181 days for Cohort II)

End point values	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[36]	24[37]		
Units: Participants				
Hemoglobin, Grade 3	0	1		
Hemoglobin, Grade 4	0	0		
Platelet count, Grade 3	0	0		
Platelet count, Grade 4	0	0		
Total Neutrophils, Grade 3	0	0		
Total Neutrophils, Grade 4	0	2		
White Blood Cell count, Grade 3	0	0		
White Blood Cell, Grade 4	0	1		

Notes:

[36] - Safety Population: all participants that took at least one dose of DTG

[37] - Safety Population: all participants that took at least one dose of DTG

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
SAEs and non-serious AEs were collected from start of study treatment until the follow-up contact.	
Adverse event reporting additional description:	
SAEs and non-serious AEs were collected in the Safety Population, comprised of all participants that took at least one dose of DTG.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Cohort I (DTG 50 mg OD)
Reporting group description:	
Participants received dolutegravir (DTG) 50 milligrams (mg) once a day (OD).	
Reporting group title	Cohort II (DTG 50 mg BID)
Reporting group description:	
Participants received DTG 50 mg twice a day (BID).	

Serious adverse events	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 27 (37.04%)	11 / 24 (45.83%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			

subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunoblastic lymphoma			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Cryoglobulinaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
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 discomfort			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			

subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain mass			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Convulsion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Febrile bone marrow aplasia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anogenital dysplasia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic fibrosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (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			
Osteoarthritis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (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			
Gastroenteritis viral			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosyphilis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
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 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Body fat disorder			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemochromatosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort I (DTG 50 mg OD)	Cohort II (DTG 50 mg BID)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)	22 / 24 (91.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			

subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 27 (11.11%)	7 / 24 (29.17%)	
occurrences (all)	4	9	
Asthenia			
subjects affected / exposed	6 / 27 (22.22%)	3 / 24 (12.50%)	
occurrences (all)	6	4	
Oedema peripheral			
subjects affected / exposed	4 / 27 (14.81%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	5	
Influenza like illness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Injection site reaction			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	15	
Malaise			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 27 (18.52%)	7 / 24 (29.17%)	
occurrences (all)	5	10	

Dyspnoea			
subjects affected / exposed	2 / 27 (7.41%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Sinus congestion			
subjects affected / exposed	0 / 27 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	7	
Oropharyngeal pain			
subjects affected / exposed	0 / 27 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Rhinorrhoea			
subjects affected / exposed	0 / 27 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Nasal congestion			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 27 (18.52%)	2 / 24 (8.33%)	
occurrences (all)	5	2	
Anxiety			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Depressed mood			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Depression			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 27 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	4	
Weight decreased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 27 (14.81%)	3 / 24 (12.50%)	
occurrences (all)	4	3	
Sciatica			
subjects affected / exposed	2 / 27 (7.41%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Dysaesthesia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 27 (7.41%)	4 / 24 (16.67%)	
occurrences (all)	2	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 27 (29.63%)	9 / 24 (37.50%)	
occurrences (all)	10	15	
Abdominal pain upper			
subjects affected / exposed	3 / 27 (11.11%)	3 / 24 (12.50%)	
occurrences (all)	5	4	
Constipation			
subjects affected / exposed	3 / 27 (11.11%)	2 / 24 (8.33%)	
occurrences (all)	4	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 27 (11.11%)	2 / 24 (8.33%)	
occurrences (all)	3	4	

Nausea			
subjects affected / exposed	2 / 27 (7.41%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	2 / 27 (7.41%)	3 / 24 (12.50%)	
occurrences (all)	6	4	
Abdominal distension			
subjects affected / exposed	2 / 27 (7.41%)	2 / 24 (8.33%)	
occurrences (all)	2	3	
Abdominal pain			
subjects affected / exposed	4 / 27 (14.81%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Anogenital dysplasia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Defaecation urgency			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Hyperhidrosis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Intertrigo			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 27 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 27 (18.52%)	2 / 24 (8.33%)	
occurrences (all)	5	2	

Back pain			
subjects affected / exposed	3 / 27 (11.11%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Myalgia			
subjects affected / exposed	4 / 27 (14.81%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Pain in extremity			
subjects affected / exposed	0 / 27 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	8	
Osteoarthritis			
subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Muscle spasms			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Tendonitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 27 (22.22%)	7 / 24 (29.17%)	
occurrences (all)	6	12	
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)	5 / 24 (20.83%)	
occurrences (all)	2	11	
Nasopharyngitis			
subjects affected / exposed	2 / 27 (7.41%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Gastroenteritis viral			
subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Influenza			
subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Oral herpes			

subjects affected / exposed	3 / 27 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	4	
Ear infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Genital herpes			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Herpes virus infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Rhinitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Tooth abscess			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hypercholesterolaemia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Vitamin D deficiency			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2009	Amendment No 1.: Inclusion of final 9-month monkey toxicology data summary, update of the study design discussion sections based on the toxicology data, clarification of definition of evidence of resistance to antiretrovirals for eligibility, addition of an inclusion criterion, addition of resistance testing at Day 1 in the time and events table with a corresponding update of the Viral Genotyping and Phenotyping Section, update on requirements for PBMC collection in the time and events table, clarification of timing of pre-dose PK samples, correction of specification of etravirine use in one section of the protocol and correction of minor typographical errors.
16 September 2009	Amendment No 2.: Clarification of instructions for pregnancy testing at Day 1 to include urine pregnancy testing, addition of text on guidance and recommendations for timing of influenza vaccine, formatting correction of table in Section 6.3, other minor clarifications and correction of typographical errors.
29 April 2010	Amendment No. 3: This amendment details the inclusion of an additional cohort of subjects to receive DTG 50 mg twice daily (Cohort II), dose-rationale and PK-PD model to evaluate potential benefit of increasing the dose of DTG, and summarizes preliminary data from ING112961 Cohort I (50 mg), safety data from ING112276, preliminary data from ING111856 (QT Study). In addition, this amendment includes other minor clarifications and corrections of typographical errors.
26 August 2010	Amendment No.4: This amendment specifies a change of Study Sponsor, provides updated safety information from ING112961 Cohort I and ING112276 and specifies additional urinalyses. Removal of chronic NSAID use from prohibited medications.
29 August 2011	Amendment No.5: This amendment is to allow ongoing Cohort I subjects the option to receive DTG 50mg BID. Efficacy and safety information from Cohort II have been provided, the prohibited medication list and toxicity management updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported