Clinical trial results:
A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults

Summary

EudraCT number	2009-018001-51
Trial protocol	ES FR BE NL GB GR IT HU PL
Global end of trial date	02 February 2021

Results information

Result version number	v2
This version publication date	12 February 2022
First version publication date	18 September 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	111762

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ViiV Healthcare
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, ViiV Healthcare, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, ViiV Healthcare, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the antiviral efficacy of GSK1349572 50 milligrams (mg) once daily compared to Raltegravir (RAL) 400 mg twice daily (BID) both in combination with a background regimen consisting of one to two (1-2) fully active single agents in human immunodeficiency virus-1 (HIV-1) infected, integrase inhibitor-naïve, therapy experienced participants at 48 weeks.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 47
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Brazil: 125
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Mexico: 41
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	South Africa: 100
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 227

Worldwide total number of subjects	719
EEA total number of subjects	93

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)	707
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted to demonstrate non-inferior antiviral activity of dolutegravir (DTG) 50 milligram (mg) once daily versus raltegravir (RAL) 400 mg twice daily in participants (pts) with human immunodeficiency viruses (HIV)-1. Long-term antiviral activity, tolerability & safety were also evaluated

Pre-assignment

Screening details:

1441 pts screened;724 randomized.719 pts received atleast 1 dose of study drug-intent to treat exposed(ITT-E)Population.5 pts didn't receive study drug(1 withdrew consent[relocated],3 non-compliant with protocol procedures,1 received prohibited drug.4pts from 1 closed site removed from ITT-E Population creating modified (m)ITT-E Population(715 pts)

Period 1

Period 1 title	Double-blind Phase (Up to Week [Wk] 48)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	DTG 50 mg OD

Arm description:

Participants received dolutegravir (DTG) 50 milligrams (mg) once daily (OD) + matching Raltegravir (RAL) placebo twice daily (BID), one in the morning (AM dose) and one in the evening (PM dose) + investigator selected background antiretroviral (ART) therapy for 48 weeks. Participants who successfully completed 48 weeks of treatment continued to have access to DTG in the Open-Label phase of the study.

Arm type	Experimental
Investigational medicinal product name	DTG 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received DTG 50 mg OD plus raltegravir placebo BID up to Week 48 during double blind (DB) phase.

Arm title	RAL 400 mg BID

Arm description:

Participants received matching DTG placebo OD + RAL 400 mg BID as AM and PM doses + investigator selected background ART therapy for 48 weeks. Participants were discontinued from the study after completion of the Week 48 visit unless a participant successfully completed Week 48 and RAL was not approved and commercially available within the country, GlaxoSmithKline (GSK) continued to supply RAL in the Open-Label Phase until commercially available.

Arm type	Active comparator
Investigational medicinal product name	RAL 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received raltegravir 400 mg BID plus DTG placebo OD up to Week 48 during the double blind phase.

Number of subjects in period 1	DTG 50 mg OD	RAL 400 mg BID
Started	357	362
Completed	299	283
Not completed	58	79
Physician decision	1	1
Consent withdrawn by subject	11	5
Site Closed	3	1
Adverse event, non-fatal	4	11
Met Protocol-Defined Stopping Criteria	5	3
Lost to follow-up	5	10
Lack of efficacy	20	42
Protocol deviation	9	6

Period 2

Period 2 title	Open-label Phase:From Wk 48 up to Wk 480
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DTG 50 mg OD

Arm description:

Participants received dolutegravir (DTG) 50 milligrams (mg) once daily (OD) + matching Raltegravir (RAL) placebo twice daily (BID), one in the morning (AM dose) and one in the evening (PM dose) + investigator selected background antiretroviral (ART) therapy for 48 weeks. Participants who successfully completed 48 weeks of treatment continued to have access to DTG in the Open-Label phase of the study.

Arm type	Experimental
Investigational medicinal product name	DTG 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants continued to receive DTG 50 mg OD in the open label phase

Arm title	RAL 400 mg BID

Arm description:

Participants received matching DTG placebo OD + RAL 400 mg BID as AM and PM doses + investigator selected background ART therapy for 48 weeks. Participants were discontinued from the study after completion of the Week 48 visit unless a participant successfully completed Week 48 and RAL was not approved and commercially available within the country, GlaxoSmithKline (GSK) continued to supply

RAL in the Open-Label Phase until commercially available.

Arm type	Active comparator
Investigational medicinal product name	RAL 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants continued to receive RAL 400 mg BID in the open label phase.

Number of subjects in period 2[1]	DTG 50 mg OD	RAL 400 mg BID
Started	295	126
Completed	227	109
Not completed	68	17
Adverse event, serious fatal	4	1
Physician decision	5	-
Consent withdrawn by subject	6	3
Adverse event, non-fatal	2	-
Met Protocol-Defined Stopping Criteria	2	-
Lost to follow-up	12	2
Lack of efficacy	27	11
Protocol deviation	10	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: For DTG arm: 4 pts completed DB Phase but did not enter OLP and for RAL arm: 157 pts completed DB Phase but did not enter OLP

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind Phase (Up to Week [Wk] 48)
Reporting group description:	
Participants were randomized to 1:1 ratio to receive dolutegravir (DTG) 50 milligram (mg) once daily or raltegravir (RAL) 400 mg twice daily for 48 Weeks	

Reporting group values	Double-blind Phase (Up to Week [Wk] 48)	Total	
Number of subjects	719	719	
Age categorical			
Baseline Characteristic data are reported for members of the modified Intent-To-Treat Exposed Population, all randomized participants who received at least one dose of IP excluding four participants at one site, which was closed due to Good Clinical Practice (GCP) non-compliance issues in another ViiV sponsored trial			
Units: Participants			
18-64 years	707	707	
From 65-84 years	12	12	
Gender categorical			
Baseline Characteristic data are reported for members of the modified Intent-To-Treat Exposed Population, all randomized participants who received at least one dose of IP excluding four participants at one site, which was closed due to Good Clinical Practice (GCP) non-compliance issues in another ViiV sponsored trial.			
Units: Subjects			
Female	230	230	
Male	485	485	
Missing	4	4	
Race/Ethnicity, Customized			
Baseline Characteristic data are reported for members of the modified Intent-To-Treat Exposed Population, all randomized participants who received at least one dose of IP excluding four participants at one site, which was closed due to Good Clinical Practice (GCP) non-compliance issues in another ViiV sponsored trial.			
Units: Subjects			
African American/African Heritage	303	303	
American Indian or Alaska Native	27	27	
Asian-Central/South Asian Heritage	4	4	
Asian-East Asian Heritage	10	10	
Asian-South East Asian Heritage	1	1	
Native Hawaiian or Other Pacific Islander	1	1	
White-Arabic/North African Heritage	6	6	
White-White/Caucasian/European Heritage	347	347	
Mixed Race	14	14	
Unknown	2	2	
Missing	4	4	
GenderNIH			
Baseline Characteristic data are reported for members of the modified Intent-To-Treat Exposed Population, all randomized participants who received at least one dose of IP excluding four participants at one site, which was closed due to Good Clinical Practice (GCP) non-compliance issues in another ViiV sponsored trial.			
Units: Subjects			

Female	230	230	
Male	485	485	
Missing	4	4	

End points

End points reporting groups

Reporting group title	DTG 50 mg OD

Reporting group description:

Participants received dolutegravir (DTG) 50 milligrams (mg) once daily (OD) + matching Raltegravir (RAL) placebo twice daily (BID), one in the morning (AM dose) and one in the evening (PM dose) + investigator selected background antiretroviral (ART) therapy for 48 weeks. Participants who successfully completed 48 weeks of treatment continued to have access to DTG in the Open-Label phase of the study.

Reporting group title	RAL 400 mg BID

Reporting group description:

Participants received matching DTG placebo OD + RAL 400 mg BID as AM and PM doses + investigator selected background ART therapy for 48 weeks. Participants were discontinued from the study after completion of the Week 48 visit unless a participant successfully completed Week 48 and RAL was not approved and commercially available within the country, GlaxoSmithKline (GSK) continued to supply RAL in the Open-Label Phase until commercially available.

Reporting group title	DTG 50 mg OD

Reporting group description:

Participants received dolutegravir (DTG) 50 milligrams (mg) once daily (OD) + matching Raltegravir (RAL) placebo twice daily (BID), one in the morning (AM dose) and one in the evening (PM dose) + investigator selected background antiretroviral (ART) therapy for 48 weeks. Participants who successfully completed 48 weeks of treatment continued to have access to DTG in the Open-Label phase of the study.

Reporting group title	RAL 400 mg BID

Reporting group description:

Participants received matching DTG placebo OD + RAL 400 mg BID as AM and PM doses + investigator selected background ART therapy for 48 weeks. Participants were discontinued from the study after completion of the Week 48 visit unless a participant successfully completed Week 48 and RAL was not approved and commercially available within the country, GlaxoSmithKline (GSK) continued to supply RAL in the Open-Label Phase until commercially available.

Primary: Percentage of participants with Human Immunodeficiency Virus-1 (HIV-1) ribonucleic acid (RNA) <50 copies/milliliter (c/mL) at Week 48

End point title	Percentage of participants with Human Immunodeficiency Virus-1 (HIV-1) ribonucleic acid (RNA) <50 copies/milliliter (c/mL) at Week 48

End point description:

Percentage of pts with Plasma HIV-1 RNA <50 c/mL at Week 48 assessed using Missing,Switch or Discontinuation=Failure (MSDF),as codified by the Food and Drug Administration (FDA)"snapshot"algorithm which treated all pts without HIV-1 RNA at Week 48 as nonresponders and pts who switched their concomitant ART prior to Week 48 as follows:background ART substitutions non-permitted per protocol(1 background ART substitution permitted for safety or tolerability);background ART substitutions permitted per protocol unless decision to switch documented as being before or at first on-treatment visit where HIV-1 RNA was assessed. Otherwise,virologic success or failure was determined by last available HIV-1 RNA assessment while pt was on-treatment in randomized phase of study.mITT-E Population:All randomized pts who received at least 1 dose of investigational product (IP) excluding 4 pts at 1 site,which closed due to Good Clinical Practice(GCP)non-compliance issues in another ViiV sponsored trial

End point type	Primary

End point timeframe:

At Week 48

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[1]	361[2]		
Units: Percentage of participants	71	64		

Notes:

[1] - Modified Intent-To-Treat Exposed (mITT-E) Population.

[2] - Modified Intent-To-Treat Exposed (mITT-E) Population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was adjusted for the BL stratification factors: HIV-1 RNA (<=50000 versus [vs]> 50000 c/mL), darunavir-ritonavir use without primary protease inhibitor mutations (yes vs no), and phenotypic susceptibility score (2 vs <2) to background regimen.

Comparison groups	DTG 50 mg OD v RAL 400 mg BID
Number of subjects included in analysis	715
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.03 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	14.2

Notes:

[3] - Non-inferiority of DTG 50 mg and RAL at Week 48 can be concluded if the lower bound of a two-sided 95% confidence interval (CI) for the difference in percentages (DTG - RAL) is greater than -12%. If non-inferiority were established, superiority would be tested at the nominal 5% level based on a pre-specified testing procedure.

[4] - P-value is for test of superiority. Adjusted difference in proportion which is based on the difference in percentage, adjusted for Baseline (BL) stratification factors.

Secondary: Number of participants (par.) with detectable virus that has genotypic or phenotypic evidence of treatment-emergent integrase inhibitor (INI) resistance at time of protocol defined virology failure (PDVF)

End point title	Number of participants (par.) with detectable virus that has genotypic or phenotypic evidence of treatment-emergent integrase inhibitor (INI) resistance at time of protocol defined virology failure (PDVF)

End point description:

For par. meeting one of the criteria for PDVF, plasma samples collected at the time point of virologic failure and Baseline were tested to evaluate any potential genotypic and/or phenotypic evolution of resistance. PDVF was defined as (A) virologic non-response: a decrease in plasma HIV-1 RNA of <1 logarithm to base 10 (log10) copies/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 copies/ mL; confirmed plasma HIV-1 RNA levels >=400 copies/mL on or after Week 24 or (B) virologic rebound: confirmed rebound in plasma HIV-1 RNA levels to >=400 copies/mL after prior confirmed suppression to <400 copies/mL; confirmed plasma HIV-1 RNA levels >1 log10 copies/mL above the nadir value, where nadir is >=400 copies/mL.Treatment-emergent IN mutations are those detected at the time of PDVF but not at Baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) until PDVF (Up to Week 48)

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[5]	361[6]		
Units: Participants	4	17		

Notes:

[5] - mITT-E Population

[6] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with plasma HIV-1 RNA <50 c/mL at Week 24

End point title	Number of participants with plasma HIV-1 RNA <50 c/mL at Week 24

End point description:

The number of participants with Plasma Human Immunodeficiency Virus-1 (HIV-1) Ribonucleic Acid (RNA) <50 c/mL at Week 24 was assessed using the Missing, Switch or Discontinuation = Failure (MSDF), as codified by the Food and Drug Administration (FDA) "snapshot" algorithm. This algorithm treated all participants without HIV-1 RNA at Week 24 as nonresponders, as well as participants who switched their concomitant ART prior to Week 24 as follows: background ART substitutions non-permitted per protocol (one background ART substitution was permitted for safety or tolerability); background ART substitutions permitted per protocol unless the decision to switch was documented as being before or at the first on-treatment visit where HIV-1 RNA was assessed. Otherwise, virologic success or failure was determined by the last available HIV-1 RNA measurement through Week 24 (within window) while the participant was on-treatment. The result below corresponds to the Week 24 interim analysis.

End point type	Secondary

End point timeframe:

At Week 24

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[7]	361[8]		
Units: Participants	281	252		

Notes:

[7] - mITT-E Population

[8] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with plasma HIV-1 RNA <400 c/mL at Week 24 and Week 48

End point title	Number of participants with plasma HIV-1 RNA <400 c/mL at Week 24 and Week 48

End point description:

The number of participants with Plasma Human Immunodeficiency Virus-1 (HIV-1) Ribonucleic Acid (RNA) <400 c/mL at the visit of interest was assessed using the Missing, Switch or Discontinuation = Failure (MSDF), as codified by the Food and Drug Administration (FDA) "snapshot" algorithm. This algorithm treated all participants without HIV-1 RNA at the visit of interest as nonresponders, as well as participants who switched their concomitant ART prior to the visit of interest as follows: background ART substitutions non-permitted per protocol (one background ART substitution was permitted for safety or tolerability); background ART substitutions permitted per protocol unless the decision to switch was documented as being before or at the first on-treatment visit where HIV-1 RNA was assessed. Otherwise, virologic success or failure was determined by the last available HIV-1 RNA measurment (within window) for the timepoint of interest while the participant was on-treatment.

End point type	Secondary

End point timeframe:

At Week 24 and Week 48

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[9]	361[10]		
Units: Participants				
Week 24	307	287		
Week 48	278	257		

Notes:

[9] - mITT-E Population

[10] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values of Cluster of Differentiation 4+ (CD4+) Cell Counts at Baseline (Day 1) and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 96 and 144

End point title	Absolute Values of Cluster of Differentiation 4+ (CD4+) Cell Counts at Baseline (Day 1) and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 96 and 144

End point description:

Blood samples were collected at specified time points to assess CD4+ using flow cytometry. Median and interquartile range are presented. Baseline was the latest pre-dose assessment value (Day 1). Only those participants with data available at the specified time points were analyzed (represented by "n=X" in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 96 and 144

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[11]	361[12]		
Units: Cells per cubic millimeter				
median (inter-quartile range (Q1-Q3))				

Baseline (Day 1), n=354, 361	204.5 (88 to 368)	193.0 (96 to 365)		
Week 4, n=341, 351	266.0 (164 to 416)	253.0 (153 to 425)		
Week 8, n=338, 346	280.0 (179 to 423)	268.0 (163 to 445)		
Week 12, n=335, 345	296.0 (188 to 451)	289.0 (174 to 443)		
Week 16, n=327, 338	299.0 (179 to 462)	293.0 (186 to 460)		
Week 24, n=326, 326	334.5 (201 to 488)	326.5 (198 to 473)		
Week 32, n=309, 309	332.0 (229 to 482)	338.0 (215 to 484)		
Week 40, n=299, 292	376.0 (239 to 523)	349.0 (227 to 500)		
Week 48, n=298, 286	387.0 (247 to 565)	378.5 (247 to 521)		
Week 96, n=260, 22	436.5 (300 to 616)	484.5 (393 to 573)		
Week 144, n=192, 18	500.0 (346 to 657)	535.0 (371 to 579)		

Notes:

[11] - mITT-E Population.

[12] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Counts at Weeks 4, 8, 12,16, 24, 32, 40, 48, 96 and 144

End point title	Change From Baseline in CD4+ Cell Counts at Weeks 4, 8, 12,16, 24, 32, 40, 48, 96 and 144

End point description:

Blood samples were collected at specified time points to assess CD4+. It was evaluated by flow cytometry. Baseline was the latest pre-dose assessment value (Day 1). Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Median and interquartile range is presented. Only those participants with data available at the specified time points were analyzed (represented by "n=X" in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 96 and 144

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[13]	361[14]		
Units: Cells per cubic millimeter				
median (inter-quartile range (Q1-Q3))				
Week 4, n=341, 351	53.0 (0 to 109)	45.0 (5 to 99)		
Week 8, n=338, 346	60.5 (15 to 117)	59.0 (12 to 124)		
Week 12, n=335, 345	74.0 (25 to 135)	75.0 (22 to 141)		

Week 16, n=327, 338	76.0 (20 to 156)	79.5 (28 to 158)		
Week 24, n=326, 326	99.0 (34 to 184)	93.0 (46 to 166)		
Week 32, n=309, 309	107.0 (49 to 188)	116.0 (52 to 173)		
Week 40, n=299, 292	125.0 (57 to 212)	117.5 (51.5 to 192)		
Week 48, n=298, 286	144.0 (73 to 239)	137.0 (65 to 222)		
Week 96, n=260, 22	198.5 (92.5 to 299.5)	270 (209 to 348)		
Week 144, n= 192, 18	243.0 (138 to 357)	302.5 (154 to 390)		

Notes:

[13] - mITT-E Population.

[14] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Post-Baseline HIV-associated Conditions, Excluding Recurrences, and Disease Progressions

End point title	Number of Participants With Post-Baseline HIV-associated Conditions, Excluding Recurrences, and Disease Progressions

End point description:

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

End point type	Secondary

End point timeframe:

Up to Week 480

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[15]	361[16]		
Units: Participants				
Any CAT	32	25		
CAT B	16	14		
CAT C	12	8		
Death	6	4		
Progression from CAT A to CAT C	2	1		
Progression from CAT B to CAT C	0	1		
Progression from CAT C to New CAT C	9	5		
Progression from CAT A, B, or C to Death	6	4		

Notes:

[15] - mITT-E Population

[16] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with post-Baseline emergent Grade 1 to 4 clinical chemistry and hematology toxicities

End point title	Number of participants with post-Baseline emergent Grade 1 to 4 clinical chemistry and hematology toxicities

End point description:

All Grade 1 to 4 post-Baseline-emergent chemistry toxicities included alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), asparate aminotransferase (AST), carbon dioxide (CO2) content/bicarbonate, cholesterol, creatine kinase (CK), creatinine, hyperglycemia, hyperkalemia, hypernatremia, hypoglycemia, hypokalemia, hyponatremia, low density lipoprotein (LDL) cholesterol calculation, lipase, total bilirubin, and triglycerides. All Grade 1 to 4 post-Baseline-emergent hematology toxities included hemoglobin, platelet count, total neutrophils, and white blood cell count. The Division of AIDS (DAIDS) defined toxicity grades as follows: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, potentially life threatening; Grade 5, death. Higher the grade, more severe the symptoms.
Safety Population:All pts who received at least 1 dose of IP (i.e., DTG or RAL)

End point type	Secondary

End point timeframe:

From Baseline (Day 1) until Week 48, including participants with post-treatment events occurring after Week 48 for participants not entering the post-Week 48 Open-Label phase of the study

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357[17]	362[18]		
Units: Participants				
ALT	47	46		
Albumin	4	3		
ALP	27	42		
AST	49	52		
CO2 content/bicarbonate	97	109		
Cholesterol	99	103		
CK	28	29		
Creatinine	18	13		
Hyperglycaemia	71	80		
Hyperkalemia	7	6		
Hypernatremia	5	7		
Hypoglycaemia	21	14		
Hypokalemia	37	41		
Hyponatremia	76	79		
LDL cholesterol calculation	68	82		
Lipase	63	68		
Total bilirubin	56	53		
Triglycerides	14	24		

Hemoglobin	19	27		
Platelet count	36	32		
Total neutrophils	49	49		
White Blood Cell count	19	29		

Notes:

[17] - Safety Population

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with post-Baseline Emergent Grade 1 to 4 Clinical Chemistry and Hematology Toxicities

End point title	Number of participants with post-Baseline Emergent Grade 1 to 4 Clinical Chemistry and Hematology Toxicities

End point description:

Blood samples were collected for the analysis of clinical chemistry and hematology parameters: Alanine aminotransferase (ALT), albumin, alkaline phosphate (ALP), aspartate aminotransferase (AST), carbon dioxide (CO2) content/bicarbonate, cholesterol, creatine kinase (CK), creatinine, hyperglycemia, hyperkalemia, hypernatremia, hypoglycemia, hypokalemia, hypoonatremia, LDL cholesterol, lipase, total bilirubin, triglycerides, hemoglibin, neutrophils, platelets, white blood cells. Any abnormality in clinical chemistry and hematology parameters were evaluated according to the DAIDS toxicity scale From Grade 1 to 4: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (Potentially life-threatening).Higher the grade, more severe the symptoms. Only those participants who completed Week 48 and continued into open-label phase were included in this analysis.

End point type	Secondary

End point timeframe:

From Week 48 to Week 480

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295[19]	126[20]		
Units: Participants				
ALT, Grades 1 to 4	36	9		
ALT, Grades 2 to 4	11	3		
ALT, Grades 3 to 4	4	0		
Albumin, Grades 1 to 4	3	0		
Albumin, Grades 2 to 4	3	0		
Albumin, Grades 3 to 4	0	0		
ALP, Grades 1 to 4	20	1		
ALP, Grades 2 to 4	4	1		
ALP, Grades 3 to 4	1	1		
AST, Grades 1 to 4	36	8		
AST, Grades 2 to 4	14	0		
AST, Grades 3 to 4	1	0		
CO2 content/bicarbonate, Grades 1 to 4	100	21		
CO2 content/bicarbonate, Grades 2 to 4	12	3		
CO2 content/bicarbonate, Grades 3 to 4	0	0		
Cholesterol, Grades 1 to 4	138	26		
Cholesterol, Grades 2 to 4	66	16		

Cholesterol, Grades 3 to 4	11	3		
CK, Grades 1 to 4	35	4		
CK, Grades 2 to 4	11	1		
CK, Grades 3 to 4	2	1		
Creatinine, Grades 1 to 4	20	2		
Creatinine, Grades 2 to 4	8	2		
Creatinine, Grades 3 to 4	2	1		
Hyperglycemia, Grades 1 to 4	94	10		
Hyperglycemia, Grades 2 to 4	40	6		
Hyperglycemia, Grades 3 to 4	7	1		
Hyperkalemia, Grades 1 to 4	9	1		
Hyperkalemia, Grades 2 to 4	4	1		
Hyperkalemia, Grades 3 to 4	2	0		
Hypernatremia, Grades 1 to 4	7	1		
Hypernatremia, Grades 2 to 4	1	0		
Hypernatremia, Grades 3 to 4	0	0		
Hypoglycemia, Grades 1 to 4	22	4		
Hypoglycemia, Grades 2 to 4	2	1		
Hypoglycemia, Grades 3 to 4	0	0		
Hypokalemia, Grades 1 to 4	29	13		
Hypokalemia, Grades 2 to 4	1	1		
Hypokalemia, Grades 3 to 4	0	0		
Hyponatremia, Grades 1 to 4	55	15		
Hyponatremia, Grades 2 to 4	2	0		
Hyponatremia, Grades 3 to 4	0	0		
LDL cholesterol, Grades 1 to 4	107	22		
LDL cholesterol, Grades 2 to 4	46	10		
LDL cholesterol, Grades 3 to 4	15	3		
Lipase, Grades 1 to 4	67	7		
Lipase, Grades 2 to 4	35	3		
Lipase, Grades 3 to 4	12	0		
Total bilirubin, Grades 1 to 4	52	11		
Total bilirubin, Grades 2 to 4	42	10		
Total bilirubin, Grades 3 to 4	18	6		
Triglycerides, Grades 1 to 4	23	2		
Triglycerides, Grades 2 to 4	23	2		
Triglycerides, Grades 3 to 4	11	1		
Hemoglobin, Grades 1 to 4	11	6		
Hemoglobin, Grades 2 to 4	6	0		
Hemoglobin, Grades 3 to 4	2	0		
Neutrophils, Grades 1 to 4	37	9		
Neutrophils, Grades 2 to 4	14	4		
Neutrophils, Grades 3 to 4	7	2		
Platelets, Grades 1 to 4	22	7		
Platelets, Grades 2 to 4	11	1		
Platelets, Grades 3 to 4	4	0		
White Blood Cells, Grades 1 to 4	17	3		
White Blood Cells, Grades 2 to 4	7	1		
White Blood Cells, Grades 3 to 4	0	0		

Notes:

[19] - Safety Population

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: DTG PK parameters including Maximum plasma drug concentration (Cmax), Minimal plasma drug concentration (Cmin), and average plasma pre-dose concentration (C0_avg)

End point title	DTG PK parameters including Maximum plasma drug concentration (Cmax), Minimal plasma drug concentration (Cmin), and average plasma pre-dose concentration (C0_avg)[21]

End point description:

Cmax, Cmin and C0_avg were assessed by population pharmacokinetic (PK) modeling using sparse PK samples which were collected as follows: one pre-dose sample and one post-dose sample at 1 to 3 hours/4 to 12 hours at Week 4, one pre-dose sample at Week 24, and one pre-dose sample and one post-dose sample at 1 to 3 hours/4 to 12 hours at Week 48. Cmax, Cmin and C0_avg were estimated and reported here. PK Concentration Population: all participants who received DTG, underwent sparse PK sampling during the study, and provided evaluable DTG plasma concentration data. Only those participants with data available at the specified data points were assessed (represented by "n=X" in the category titles).

End point type	Secondary

End point timeframe:

Pre-dose and at 1 to 3 hours or 4 to 12 hours post-dose at Week 4; Pre-dose at Week 24; Pre-dose and 1 to 3 hours or 4 to 12 hours post-dose at Week 48

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were only calculated for DTG arm in double blind phase

End point values	DTG 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	342[22]			
Units: microgram/milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
C0_avg, n=342	0.926 (± 131)			
Cmax, n=340	3.21 (± 26.7)			
Cmin, n=340	0.849 (± 76.5)			

Notes:

[22] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: DTG PK parameter including pre-dose concentration (C0)

End point title	DTG PK parameter including pre-dose concentration (C0)[23]

End point description:

C0 was assessed by population PK modeling using sparse PK samples which were collected as follows: one pre-dose sample and one post-dose sample at 1 to 3 hours/4 to 12 hours at Week 4, one pre-dose sample at Week 24, and one pre-dose sample and one post-dose sample at 1 to 3 hours/4 to 12 hours at Week 48. DTG predose concentration (C0) at Week 4, Week 24, and Week 48 was estimated and reported here. Only those participants with data available at the specified data points were assessed (represented by "n=X" in the category titles).

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 4, 24 and 48

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were only calculated for DTG arm in double blind phase

End point values	DTG 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	342[24]			
Units: microgram/milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Week 4, n=329	0.786 (± 143)			
Week 24, n=298	0.940 (± 132)			
Week 48, n=276	0.932 (± 152)			

Notes:

[24] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: DTG PK parameters including area under the plasma concentration-time curve from time zero to time tau over a dosing interval at steady state (AUC[0-tau])

End point title	DTG PK parameters including area under the plasma concentration-time curve from time zero to time tau over a dosing interval at steady state (AUC[0-tau])[25]

End point description:

AUC is defined as the area under the DTG concentration-time curve as a measure of drug exposure over time. AUC(0-tau) is defined as the area under the plasma concentration-time curve from time zero to time tau over a dosing interval at steady state, where tau is the length of the dosing interval of DTG. AUC was assessed by population pharmacokinetic (PK) modeling using sparse PK samples which were collected as follows: one pre-dose sample and one post-dose sample at 1 to 3 hours/4 to 12 hours at Week 4, one pre-dose sample at Week 24, and one pre-dose sample and one post-dose sample at 1 to 3 hours/4 to 12 hours at Week 48. PK Concentration Population: all participants who received DTG, underwent sparse PK sampling during the study, and provided evaluable DTG plasma concentration data. Only those participants available at the indicated time points were assessed.

End point type	Secondary

End point timeframe:

Pre-dose and at 1 to 3 hours or 4 to 12 hours post-dose at Week 4; Pre-dose at Week 24; Pre-dose and 1 to 3 hours or 4 to 12 hours post-dose at Week 48

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were only calculated for DTG arm in double blind phase

End point values	DTG 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	340[26]			
Units: Micrograms*hour/milliliter (µg*hr/mL)				
geometric mean (geometric coefficient of variation)	44.7 (± 40.5)			

Notes:

[26] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimensions-3 Levels (EQ-5D-3L) Utility Score

End point title	Change From Baseline in European Quality of Life-5 Dimensions-3 Levels (EQ-5D-3L) Utility Score

End point description:

The EQ-5D-3L questionnaire provides a profile of participant function and a global health state rating. The five-item measure has one question assessing each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 3 levels for each dimension including 1=no problems, 2=some problems, 3=extreme problems. The health state is defined by combining the levels of answers from each of the 5 questions. Each health state is referred to in terms of a 5 digit code. Health state 5 digit code is translated into utility score, which is valued up to 1 (perfect health) with lower values meaning worse state. EQ-5D-3L utility score ranges from -0.594 to 1. Higher scores indicate better health. Baseline was the latest pre-dose assessment value (Day 1) and change from Baseline=post-dose value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Weeks 24 and 48

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[27]	361[28]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 24, n=350, 356	0.010 (± 0.202)	0.019 (± 0.204)		
Week 48, n=350, 356	0.028 (± 0.179)	0.013 (± 0.222)		

Notes:

[27] - mITT-E Population.

[28] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimensions-3 Levels (EQ-5D-3L) thermometer scores

End point title	Change From Baseline in European Quality of Life-5

	Dimensions-3 Levels (EQ-5D-3L) thermometer scores

End point description:

The EQ-5D-3L questionnaire provides a profile of participant function and a global health state rating. The five-item measure has one question assessing each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 3 levels for each dimension including 1=no problems, 2=some problems, 3=extreme problems. EQ-5D-3L included EQ visual Analogue scale (EQ VAS) 'Thermometer' which provided Self-rated current health status. Participants were asked to rate their current health status using the visual analogue scale 'Thermometer'. Score ranged from 0 (worst imaginable health state) to 100 (best imaginable health state). Higher scores indicate better heath. Baseline was the latest pre-dose assessment value (Day 1) and change from Baseline=post-dose value minus Baseline value. Only those participants with data available at the specified data points were assessed (represented by "n=X" in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Weeks 24 and 48

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354[29]	361[30]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 24, n=350, 355	6.800 (± 21.413)	4.645 (± 18.279)		
Week 48, n=350, 355	8.894 (± 20.356)	5.597 (± 18.821)		

Notes:

[29] - mITT-E Population.

[30] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Absolute values of cluster of differentiation 8+ (CD8+) cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point title	Absolute values of cluster of differentiation 8+ (CD8+) cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point description:

The absolute value data for CD8+ cell count was planned to be evaluated. This was an other pre-specified outcome measure. The results for this outcome measure will never be posted.

End point type	Other pre-specified

End point timeframe:

At Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[31]	0[32]		
Units: Cells per cubic millimeters				
median (inter-quartile range (Q1-Q3))	(to)	(to)		

Notes:

[31] - mITT-E Population.

[32] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in CD8+ cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point title	Change from Baseline in CD8+ cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point description:

Change from Baseline data for CD8+ cell count was planned to be evaluated. This was an other pre-specified outcome measure. The results for this outcome measure will never be posted.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1); Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point values	DTG 50 mg OD	RAL 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[33]	0[34]		
Units: Cells per cubic millimeters				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[33] - mITT-E Population.

[34] - mITT-E Population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs), non-serious AEs and all-cause mortality were collected from the start of study medication to the end of the study (up to Week 480)

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	RAL~400mg BID

Reporting group description:

Participants received matching DTG placebo OD + RAL 400 mg BID as AM and PM doses + investigator selected background ART therapy for 48 weeks. Participants were discontinued from the study after completion of the Week 48 visit unless a participant successfully completed Week 48 and RAL was not approved and commercially available within the country, GSK continued to supply RAL in the Open-Label Phase until it was commercially available.

Reporting group title	DTG~50mg QD

Reporting group description:

Participants received dolutegravir (DTG) 50 milligrams (mg) once daily (OD) + matching Raltegravir (RAL) placebo twice daily (BID), one in the morning (AM dose) and one in the evening (PM dose) + investigator selected background antiretroviral (ART) therapy for 48 weeks. Participants who successfully completed 48 weeks of treatment continued to have access to DTG in the Open-Label phase of the study.

Serious adverse events	RAL~400mg BID	DTG~50mg QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 362 (12.71%)	73 / 357 (20.45%)	
number of deaths (all causes)	4	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immunoblastic lymphoma			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval neoplasm			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anogenital warts			
subjects affected / exposed	0 / 362 (0.00%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal neoplasm			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal adenocarcinoma			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hodgkin's disease			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (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 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
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			
Alveolar proteinosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus disorder			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasal valve collapse			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 362 (0.28%)	4 / 357 (1.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance abuse			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back injury			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine perforation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Cerebrovascular disorder			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
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	2 / 362 (0.55%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation factor deficiency			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Methaemoglobinaemia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Iritis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral mucosal blistering			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver disorder			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 362 (0.28%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 362 (1.93%)	7 / 357 (1.96%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 362 (0.55%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus oesophagitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapulmonary tuberculosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas gangrene			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis disseminated			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective myositis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 362 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus infection			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis liver			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes simplex			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral toxoplasmosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 362 (0.55%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 362 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RAL~400mg BID	DTG~50mg QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 362 (56.91%)	250 / 357 (70.03%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 362 (4.14%)	39 / 357 (10.92%)	
occurrences (all)	16	43	
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 362 (9.94%)	43 / 357 (12.04%)	
occurrences (all)	41	57	
Dizziness			
subjects affected / exposed	13 / 362 (3.59%)	20 / 357 (5.60%)	
occurrences (all)	13	21	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 362 (7.18%)	19 / 357 (5.32%)	
occurrences (all)	29	21	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	64 / 362 (17.68%)	92 / 357 (25.77%)	
occurrences (all)	86	134	
Nausea			
subjects affected / exposed	31 / 362 (8.56%)	35 / 357 (9.80%)	
occurrences (all)	38	41	
Vomiting			

subjects affected / exposed	20 / 362 (5.52%)	27 / 357 (7.56%)	
occurrences (all)	30	32	
Abdominal pain			
subjects affected / exposed	8 / 362 (2.21%)	21 / 357 (5.88%)	
occurrences (all)	8	24	
Abdominal pain upper			
subjects affected / exposed	5 / 362 (1.38%)	23 / 357 (6.44%)	
occurrences (all)	5	25	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 362 (7.18%)	46 / 357 (12.89%)	
occurrences (all)	31	61	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	21 / 362 (5.80%)	30 / 357 (8.40%)	
occurrences (all)	21	34	
Psychiatric disorders			
Depression			
subjects affected / exposed	7 / 362 (1.93%)	18 / 357 (5.04%)	
occurrences (all)	7	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 362 (7.46%)	34 / 357 (9.52%)	
occurrences (all)	29	38	
Back pain			
subjects affected / exposed	16 / 362 (4.42%)	30 / 357 (8.40%)	
occurrences (all)	17	37	
Pain in extremity			
subjects affected / exposed	20 / 362 (5.52%)	23 / 357 (6.44%)	
occurrences (all)	24	25	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	37 / 362 (10.22%)	72 / 357 (20.17%)	
occurrences (all)	82	168	
Influenza			

subjects affected / exposed	34 / 362 (9.39%)	42 / 357 (11.76%)	
occurrences (all)	50	69	
Nasopharyngitis			
subjects affected / exposed	22 / 362 (6.08%)	43 / 357 (12.04%)	
occurrences (all)	23	67	
Urinary tract infection			
subjects affected / exposed	20 / 362 (5.52%)	35 / 357 (9.80%)	
occurrences (all)	24	43	
Sinusitis			
subjects affected / exposed	17 / 362 (4.70%)	31 / 357 (8.68%)	
occurrences (all)	20	41	
Bronchitis			
subjects affected / exposed	15 / 362 (4.14%)	27 / 357 (7.56%)	
occurrences (all)	18	45	
Gastroenteritis			
subjects affected / exposed	7 / 362 (1.93%)	21 / 357 (5.88%)	
occurrences (all)	9	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2010	Amendment 1: Country Specific Amendment for the United Kingdom
14 January 2011	Amendment 2: Primary reasons for this amendment include the addition of a Week 2 visit for all participants, and reference to an independent data monitoring committee (IDMC) which will regularly review targeted safety information; text was also added to allow use of entecavir for treatment of hepatitis B in appropriate clinical situations; minor clarifications and corrections have also been incorporated.
15 April 2011	Amendment 3: Country Specific Amendment for South Africa
29 August 2011	Amendment 4: Primary reasons for this amendment include: allowing the use of historical resistance test result in participants off antiretroviral therapy (ART) for at least one month to determine eligibility, adding text for rash management; text added for withdrawal based on new rash management wording; modification of text on decline in renal function; adding syphilis screening, drugs of abuse (including alcohol) screening, and serum cetaminophen test to liver event follow-up assessments; adding possible Week 24 group-sequential analysis; clarification regarding Missing, Switch or Discontinuation=Failure (MSDF) algorithm; change for hepatitis B and C serology collection at Screening versus (vs) current Day 1 collection; allow co-administration of fosamprenavir with investigational products; unknown impact on efficacy if multivitamin/iron supplements are used with other medications that may decrease GSK1349572 exposure; and adding exceptions to Child Pugh Classificaton for anticoagulation therapy and use of atazanavir in failing background therapy; and updated section on publication of study results
09 September 2011	Amendment 5: This amendment is implemented to correct a formatting error in the Inclusion Criteria (Inclusion criteria #4 was incorrectly split into #4 and #5 when Amendment 04 was published); a couple minor clarifications are also included.
22 March 2012	Amendment 6: This amendment is implemented to update the prohibited medication information (rifabutin, pioglitazone, troglitazone, modafinil deleted; rifapentine added; text edited for glucocorticoids and immunomodulators); to allow a change in background therapy after Week 48 if required for tolerability/toxicity management; to allow the use of telbivudine for hepatitis B treatment; to add guidance for electronic case report form (eCRF) collection for missing visits and for reporting participants as lost to follow-up; to allow the use of pill boxes for up to 7 days; to provide clarification of when repeat pharmacokinetic (PK) samples should be collected for Week 24 and Week 48; and to inform that a group-sequential analysis is no longer planned for the study. Details regarding the medical monitor are also added. There is also a minor clarification regarding drug formulation and correction of a typographical error
09 October 2012	Amendment 7: Country Specific Amendment for South Africa
21 February 2013	Amendment 8: This amendment was implemented to allow GSK1349572 50 mg twice daily dosing for participants receiving efavirenz, tipranavir/ritonavir, rifampin, or rifapentine; updated drug drug interaction section; rifampin and rifapentine were also removed from the prohibited medication listing; abbreviation listing and references updated.

19 May 2015	Amendment 9: Country Specific Amendment for South Africa
10 July 2018	Amendment 10: Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir at the time of conception. The Risk Assessment table was updated to include language regarding risk and mitigation of neural tube defects. Inclusion criterion #2 was updated to exclude the double barrier method of contraception, which does not meet updated GSK/ViiV criteria for a highly effective method. The withdrawal criteria were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study. The Time and Events table was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy. Administrative updates were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported