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	

Results information

Result version number	v1
This version publication date	18 September 2020
First version publication date	18 September 2020

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, TW8 9GS
Public contact	GSK Response Center, ViiV Healthcare, 1 8664357343, GSKClinicalSupportHD@GSK.com
Scientific contact	GSK Response Center, ViiV Healthcare, 1 8664357343,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	22 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2013
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the antiviral efficacy of GSK1349572 50 mg once daily compared to RAL 400 mg BID both in combination with a background regimen consisting of one to two (1-2) fully active single agents in HIV-1 infected, integrase inhibitor-naïve, therapy experienced subjects 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	99

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: -

Pre-assignment

Screening details:

1441 participants were screened; 724 were randomized. A total of 719 participants received at least 1 dose of study medication and comprised the intent-to-treat exposed (ITT-E) population. Four participants from one closed site were removed from the ITT-E population creating the modified ITT-E population with 715 participants.

Period 1

Period 1 title	48 Week Double-blind Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, 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 continue to have access to DTG in the Open-Label phase of the study.

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

Dosage and administration details:

Participants received GSK1349572 50mg OD plus raltegravir placebo BID.

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, GSK will continue to supply RAL in the Open-Label Phase until it is commercially available.

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

Dosage and administration details:

Subjects received raltegravir 400mg BID plus GSK1349572 placebo OD.

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
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 continue to have access to DTG in the Open-Label phase of the study.

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

Dosage and administration details:

Participants will receive
GSK1349572 50mg OD plus
raltegravir placebo BID.

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, GSK will continue to supply RAL in the Open-Label Phase until it is commercially available.

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

Dosage and administration details:

Subjects will receive raltegravir 400mg BID plus GSK1349572 placebo OD.

Number of subjects in period 2[1]	DTG 50 mg OD	RAL 400 mg BID
Started	295	27
Ongoing at the time of analysis	282	23
Completed	0	1
Not completed	295	26
Consent withdrawn by subject	1	-
Lost to follow-up	3	-
Lack of efficacy	7	3
Protocol deviation	2	-
Ongoing at the time of analysis	282	23

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: A total of 322 out of 582 participants who completed double-blinded phase opted to continue open-label phase.

Baseline characteristics

Reporting groups	
Reporting group title	48 Week Double-blind Phase
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	48 Week Double-blind Phase	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: Subjects			
Age continuous			
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: years			
arithmetic mean	42.5		
standard deviation	± 10.13	-	
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			
Male	485	485	
Female	230	230	
Missing	4	4	
Race/Ethnicity, Customized			
Measure Description: 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	

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 continue 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, GSK will continue to supply RAL in the Open-Label Phase until it is 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 continue 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, GSK will continue to supply RAL in the Open-Label Phase until it is commercially available.

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

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

End point description:

The percentage of participants with Plasma Human Immunodeficiency Virus-1 (HIV-1) Ribonucleic Acid (RNA) <50 c/mL at Week 48 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 48 as nonresponders, as well as participants who switched their concomitant ART prior to Week 48 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 assessment while the participant was on-treatment in the randomized phase of the study.

End point type	Primary

End point timeframe:

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] - mITT-E Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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.

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] - Analysis was adjusted for the BL stratification factors: HIV-1 RNA (<=50000 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.

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

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

End point description:

The percentage 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:

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: Percentage of participants	79	70		

Notes:

[7] - mITT-E Population

[8] - mITT-E Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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
P-value	= 0.003 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	15.9

Notes:

[9] - 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: Percentage of participants with plasma HIV-1 RNA <400 c/mL at Week 24 and Week 48

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

End point description:

The percentage 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:

Week 24, 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[10]	361[11]		
Units: Percentage of Participants				
Week 24	86	79		
Week 48	79	71		

Notes:

[10] - mITT-E Population

[11] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values and change from Baseline in cluster of differentiation 4+ (CD4+) cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point title	Absolute values and change from Baseline in cluster of

	differentiation 4+ (CD4+) cell counts at Weeks 4, 8, 12, 16, 24, 32, 40, and 48

End point description:

The absolute value for CD4+ cell count (cells per millimeters cubed [mm^3]) was assessed at Baseline (BL), Week 4, Week 8, Week 12, Week 16, Week 24, Week 32, Week 40 and Week 48. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants available at the indicated time points were assessed. Only those participants available at indicated time points were represented by n=X, X in the category titles.

End point type	Secondary

End point timeframe:

Baseline; 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	354[12]	361[13]		
Units: cells/mm^3				
median (inter-quartile range (Q1-Q3))				
Absolute value, BL, n=354, 361	204.5 (88 to 368)	193.0 (96 to 365)		
Absolute value, Week 4, n=341, 351	266.0 (164 to 416)	253.0 (153 to 425)		
Absolute value, Week 8, n=338, 346	280.0 (179 to 423)	268.0 (163 to 445)		
Absolute value, Week 12, n=335, 345	296.0 (188 to 451)	289.0 (174 to 443)		
Absolute value, Week 16, n=327, 338	299.0 (179 to 462)	293.0 (186 to 460)		
Absolute value, Week 24, n=326, 326	334.5 (201 to 488)	326.5 (198 to 473)		
Absolute value, Week 32, n=309, 309	332.0 (229 to 482)	338.0 (215 to 484)		
Absolute value, Week 40, n=299, 292	376.0 (239 to 523)	349.0 (227 to 500)		
Absolute value, Week 48, n=294, 283	385.0 (244 to 565)	379.0 (250 to 521)		
Change from BL, Week 4, n=341, 351	53.0 (0 to 109)	45.0 (5 to 99)		
Change from BL, Week 8, n=338, 346	60.5 (15 to 117)	59.0 (12 to 124)		
Change from BL, Week 12, n=335, 345	74.0 (25 to 135)	75.0 (22 to 141)		
Change from BL, Week 16, n=327, 338	76.0 (20 to 156)	79.5 (28 to 158)		
Change from BL, Week 24, n=326, 326	99.0 (34 to 184)	93.0 (46 to 166)		
Change from BL, Week 32, n=309, 309	107.0 (49 to 188)	116.0 (52 to 173)		
Change from BL, Week 40, n=299, 292	125.0 (57 to 212)	117.5 (52 to 192)		
Change from BL, Week 48, n=294, 283	144.0 (73 to 242)	137.0 (67 to 224)		

Notes:

[12] - mITT-E Population

[13] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with indicated post-Baseline HIV-associated conditions, excluding recurrences, and disease progressions

End point title	Number of participants with indicated post-Baseline HIV-associated conditions, excluding recurrences, and disease progressions

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline (Day 1) until 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[14]	361[15]		
Units: Participants				
Any CAT	20	19		
CAT B	11	11		
CAT C	10	6		
Death	0	3		
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	8	3		
Progression from CAT A, B, or C to Death	0	3		

Notes:

[14] - mITT-E Population

[15] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated post-Baseline emergent Grade 1 to 4 clinical chemistry and hematology toxicities/laboratory adverse events (AEs)

End point title	Number of participants with the indicated post-Baseline emergent Grade 1 to 4 clinical chemistry and hematology toxicities/laboratory adverse events (AEs)

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. .

End point type	Secondary

End point timeframe:

From Baseline 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[16]	362[17]		
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:

[16] - mITT-E Population

[17] - mITT-E Population

Statistical analyses

No statistical analyses for this end point

Secondary: DTG PK parameters including Cmax, Cmin, C0, and C0_avg

End point title	DTG PK parameters including Cmax, Cmin, C0, and C0_avg[18]

End point description:

The maximal concentration (Cmax), and the minimal concentration (Cmin) 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. DTG predose concentration (C0) at Week 4, Week 24, and Week 48 as well as the average C0

(C0_avg) , Cmax and Cmin 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 available at indicated time points were represented by n=X, X in the category titles.

End point type	Secondary

End point timeframe:

Week 4, Week 24, and Week 48

Notes:

[18] - 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: There are no statistical data to report

End point values	DTG 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	342[19]			
Units: microgram/milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
C0, Week 4, Pre-dose, n=329	0.786 (± 143)			
C0, Week 24, Pre-dose, n=298	0.940 (± 132)			
C0, Week 48, Pre-dose, n=276	0.932 (± 152)			
C0_avg, n=342	0.926 (± 131)			
Cmax, n=340	3.21 (± 26.7)			
Cmin, n=340	0.849 (± 76.5)			

Notes:

[19] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

Secondary: DTG PK parameters including AUC(0-tau)

End point title	DTG PK parameters including AUC(0-tau)[20]

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.

End point type	Secondary

End point timeframe:

Week 4, Week 24, and Week 48

Notes:

[20] - 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: There are no statistical data to report

End point values	DTG 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	340[21]			
Units: Micrograms*hour per milliliter(µg*hr/mL)				
geometric mean (geometric coefficient of variation)	44.7 (± 40.5)			

Notes:

[21] - PK Concentration Population

Statistical analyses

No statistical analyses for this end point

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

End point title	Absolute values and change from Baseline in 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 (cells per millimeters cubed [mm^3]) were only reported on a per-participant basis and were not summarized.

End point type	Other pre-specified

End point timeframe:

Baseline; 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[22]	0[23]		
Units: cells/mm^3				
median (inter-quartile range (Q1-Q3))	(to)	(to)		

Notes:

[22] - Data was not summarized

[23] - Data was not summarized

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication to the end of the randomized treatment period (up to Week 48).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all participants who received at least one dose of investigational product. Also included are post-treatment events occurring after Week 48 for participants not entering the post-Week 48 Open-Label phase of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

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, GSK will continue to supply RAL in the Open-Label Phase until it is 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 continue to have access to DTG in the Open-Label phase of the study.

Serious adverse events	RAL 400 mg BID	DTG 50 mg OD	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 362 (11.60%)	33 / 357 (9.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
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	
Cervix carcinoma			
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	

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	
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%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 arterial occlusive 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	
General disorders and administration			

site conditions			
Non-cardiac chest pain			
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	
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	
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	
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	
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	
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%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
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	
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	
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	
Cardiac disorders			
Angina pectoris			
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	
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	
Nervous system disorders			
Cerebrovascular accident			
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	
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	
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	

Blood and lymphatic system disorders			
Anaemia			
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	
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	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 362 (0.28%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
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 acute			
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	
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	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 362 (0.28%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
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	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 362 (0.28%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
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	
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	

Back 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	
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	
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	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 362 (1.10%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
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	
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	
Bronchopneumonia			

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	
Cellulitis			
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	
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	
Genital herpes			

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	
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	
Legionella 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	
Lower respiratory tract 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	
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	
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	
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	
Lung 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			
Dehydration			
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	
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	
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	

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

Non-serious adverse events	RAL 400 mg BID	DTG 50 mg OD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 362 (47.79%)	178 / 357 (49.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 362 (8.29%)	33 / 357 (9.24%)	
occurrences (all)	34	37	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	24 / 362 (6.63%)	15 / 357 (4.20%)	
occurrences (all)	25	15	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	64 / 362 (17.68%)	71 / 357 (19.89%)	
occurrences (all)	80	96	
Nausea			
subjects affected / exposed	29 / 362 (8.01%)	29 / 357 (8.12%)	
occurrences (all)	36	31	
Vomiting			
subjects affected / exposed	20 / 362 (5.52%)	20 / 357 (5.60%)	
occurrences (all)	30	22	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 362 (6.63%)	33 / 357 (9.24%)	
occurrences (all)	26	35	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	18 / 362 (4.97%)	19 / 357 (5.32%)	
occurrences (all)	18	21	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	29 / 362 (8.01%)	38 / 357 (10.64%)	
occurrences (all)	41	44	
Influenza			
subjects affected / exposed	25 / 362 (6.91%)	24 / 357 (6.72%)	
occurrences (all)	31	34	
Nasopharyngitis			

subjects affected / exposed	22 / 362 (6.08%)	23 / 357 (6.44%)	
occurrences (all)	23	32	
Urinary tract infection			
subjects affected / exposed	18 / 362 (4.97%)	26 / 357 (7.28%)	
occurrences (all)	22	27	

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 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 MSDF algorithm; change for hepatitis B and C serology collection at Screening 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 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 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