Clinical trial results:
A Phase 3 Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Doravirine (MK-1439) 100 mg Once Daily Versus Darunavir 800 mg Once Daily plus Ritonavir 100 mg Once Daily, Each in Combination with TRUVADA™ or EPZICOM™/KIVEXA™, in Treatment-Naïve HIV-1 Infected Subjects

Summary

EudraCT number	2014-001127-69
Trial protocol	AT GB DE DK ES RO PT IT
Global end of trial date	06 March 2023

Results information

Result version number	v1 (current)
This version publication date	13 March 2024
First version publication date	13 March 2024

Trial information

Trial identification

Sponsor protocol code	1439-018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02275780
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	06 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2015
Global end of trial reached?	Yes
Global end of trial date	06 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish a new treatment option for treatment-naïve participants with HIV-1, the efficacy and safety of doravirine will be determined relative to a protease inhibitor (PI). Participants will receive double-blind treatment during 96-week Base Study. Eligible participants in Base Study will continue to receive doravirine-containing regimen open-label for additional 96 weeks in Study Ext 1. Eligible participants deriving benefit will continue in Study Extensions 2 and 3 to receive doravirine-containing regimen open-label until doravirine becomes locally available or for additional 96 weeks, whichever comes first. The Primary hypothesis is that doravirine 100 mg once a day (q.d.) is non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by proportion of participants with HIV-1 ribonucleic acid (RNA) <50 copies/mL at Week 48.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
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: 16
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Chile: 55
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Romania: 29
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	South Africa: 45
Country: Number of subjects enrolled	Spain: 76
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	United States: 267

Worldwide total number of subjects	769
EEA total number of subjects	230

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)	762
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1027 participants were screened and 769 were randomized.

Period 1

Period 1 title	Base Study: 96 weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Doravirine 100 mg

Arm description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

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

Dosage and administration details:

Doravirine 100 mg tablet administered p.o. q.d.

Investigational medicinal product name	TRUVADA™ or EPZICOM™/KIVEXA™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The investigator selects either TRUVADA™, a tablet containing 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate p.o. q.d. or EPZICOM™/KIVEXA™, a tablet containing 600 mg abacavir sulfate and 300 mg lamivudine, p.o. q.d.

Arm title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Arm description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Active comparator

Investigational medicinal product name	Darunavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Darunavir 800 mg tablet administered p.o. q.d.

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ritonavir 100 mg tablet administered p.o. q.d.

Investigational medicinal product name	TRUVADA™ or EPZICOM™/KIVEXA™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The investigator selects either TRUVADA™, a tablet containing 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate p.o. q.d. or EPZICOM™/KIVEXA™, a tablet containing 600 mg abacavir sulfate and 300 mg lamivudine, p.o. q.d.

Number of subjects in period 1	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg
Started	385	384
Treated	383	383
Completed	292	273
Not completed	93	111
Adverse event, serious fatal	3	1
Consent withdrawn by subject	19	22
Physician decision	2	4
Randomized not treated	2	1
Adverse event, non-fatal	6	14
Pregnancy	2	1
Noncompliance with drug	9	6
Lost to follow-up	28	24
Lack of efficacy	21	32
Protocol deviation	1	6

Period 2

Period 2 title	Study Extension 1: Week 96 to Week 192
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Doravirine 100 mg

Arm description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Combination therapy

No investigational medicinal product assigned in this arm

Arm title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Arm description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Combination therapy

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg
Started	259	233
Completed	210	190
Not completed	49	43
Availability of study medication locally	2	-
Physician decision	3	7
Consent withdrawn by subject	19	14
Adverse event, non-fatal	6	1
Pregnancy	2	1
Non-compliance with study drug	1	2
Lost to follow-up	8	7
Lack of efficacy	8	11

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: Not all participants enrolled in Ext 1.

Period 3

Period 3 title	Study Extension 2: Week 192 to Week 288
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Doravirine 100 mg

Arm description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Combination therapy

No investigational medicinal product assigned in this arm

Arm title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Arm description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Combination therapy

No investigational medicinal product assigned in this arm

Number of subjects in period 3[2]	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg
Started	148	129
Completed	101	91
Not completed	47	38
Availability of study medication locally	38	29
Physician decision	1	1
Consent withdrawn by subject	4	3
Adverse event, non-fatal	-	1
Non-compliance with study drug	2	-
Lost to follow-up	-	1
Lack of efficacy	2	3

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all participants enrolled in Ext 2.

Period 4

Period 4 title	Study Extension 3: Week 288 to Week 384
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Doravirine 100 mg

Arm description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Combination therapy

No investigational medicinal product assigned in this arm

Arm title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Arm description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Arm type	Combination therapy

No investigational medicinal product assigned in this arm

Number of subjects in period 4[3]	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg
Started	50	36
Completed	36	23
Not completed	14	13
Availability of study medication locally	6	6
Adverse event, serious fatal	-	1
Physician decision	1	-
Consent withdrawn by subject	5	2
Non-compliance with study drug	1	1
Lost to follow-up	1	3

Notes:

[3] - 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: Not all participants enrolled in Ext 3.

Baseline characteristics

Reporting groups	
Reporting group title	Doravirine 100 mg
Reporting group description:	
Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.	
Reporting group title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg
Reporting group description:	
Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.	

Reporting group values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg	Total
Number of subjects	385	384	769
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	34.9	35.7	
standard deviation	± 10.7	± 10.7	-
Sex: Female, Male Units: Participants			
Female	65	58	123
Male	320	326	646
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	3	6
Asian	7	7	14
Native Hawaiian or Other Pacific Islander	1	2	3
Black or African American	87	89	176
White	281	280	561
More than one race	6	2	8
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	93	86	179
Not Hispanic or Latino	286	291	577
Unknown or Not Reported	6	7	13

Plasma HIV-1 RNA			
Plasma HIV-1 RNA levels were quantified with the Abbott RealTime HIV-1 Assay and included all participants who had baseline data.			
Units: Copies/mL			
median	27073.0	27357.0	
full range (min-max)	105 to 2776658	235 to 3272236	-
Mean Cluster of Differentiation 4 (CD4+) T-cell Count			
CD4+ T-cell count was quantified by a central laboratory using a commercially available assay and included all participants who had baseline data.			
Units: Cells/mm^3			
arithmetic mean	432.6	411.9	
standard deviation	± 208.4	± 229.6	-

End points

End points reporting groups

Reporting group title	Doravirine 100 mg

Reporting group description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Reporting group description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Doravirine 100 mg

Reporting group description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Reporting group description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Doravirine 100 mg

Reporting group description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Reporting group description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Doravirine 100 mg

Reporting group description:

Double-blind Doravirine 100 mg administered orally (p.o.) once daily (q.d.) + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Reporting group description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the same treatment regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Subject analysis set title	Doravirine 100 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Double-blind Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study.

Subject analysis set title	Daurunavir 800 mg + Ritonavir 100 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study.

Primary: Percentage of Participants Achieving Plasma HIV-1 RNA <50 Copies/mL at Week 48

End point title	Percentage of Participants Achieving Plasma HIV-1 RNA <50 Copies/mL at Week 48

End point description:

The percentage of participants in each arm achieving HIV-1 RNA levels <50 copies/mL at Week 48 was determined. Plasma HIV-1 RNA levels were quantified with the Abbott RealTime HIV-1 Assay. Data were handled according to the US Food and Drug Administration (FDA) "snapshot" approach and all missing data were considered treatment failures, regardless of the reason. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of participants				
number (not applicable)	83.8	79.9		

Statistical analyses

Statistical analysis title	% Achieving PL HIV-1 RNA <50 Copies/mL at Week 96
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	766
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment Difference
Point estimate	3.913

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	9.415

Notes:

[1] - Doravirine is concluded to be non-inferior to darunavir + ritonavir if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Secondary: Percentage of Participants Achieving Plasma HIV-1 RNA <50 Copies/mL at Week 96

End point title	Percentage of Participants Achieving Plasma HIV-1 RNA <50 Copies/mL at Week 96

End point description:

The percentage of participants in each arm achieving HIV-1 RNA levels <50 copies/mL at Week 96 was determined. Plasma HIV-1 RNA levels were quantified with the Abbott RealTime HIV-1 Assay. Data were handled according to the US Food and Drug Administration (FDA) "snapshot" approach and all missing data were considered treatment failures, regardless of the reason. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had data for the outcome measure. Participants with missing HIV-1 RNA due to an Abbott RealTime manufacturing agent recall were excluded from the analysis.

End point type	Secondary

End point timeframe:

Week 96

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	379	376		
Units: Percentage of participants				
number (not applicable)	73.1	66.0		

Statistical analyses

Statistical analysis title	% Achieving PL HIV-1 RNA <50 Copies/mL at Week 96
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	755
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Treatment Difference
Point estimate	7.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.508
upper limit	13.656

Notes:

[2] - Doravirine is concluded to be non-inferior to darunavir + ritonavir if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Secondary: Change from Baseline in Mean CD4+ T-cell Count at Week 48

End point title	Change from Baseline in Mean CD4+ T-cell Count at Week 48

End point description:

CD4+ T-cell counts were quantified by a central laboratory using a commercially available assay. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had data for the outcome measure. Baseline values were carried forward for participants who discontinued therapy due to lack of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	363	353		
Units: Cells/mm^3				
arithmetic mean (confidence interval 95%)	192.7 (171.5 to 213.9)	185.6 (167.5 to 203.6)		

Statistical analyses

Statistical analysis title	Chg from BL in Mean CD4+ T-cell Count at Wk 48
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	716
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean treatment difference
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	35

Secondary: Mean Change from Baseline in Fasting Low Density Lipoprotein Cholesterol (LDL-C) at Week 48

End point title	Mean Change from Baseline in Fasting Low Density Lipoprotein Cholesterol (LDL-C) at Week 48

End point description:

Serum LDL-C was determined after an overnight fast. Change from Baseline was analyzed using ANCOVA models with terms for Baseline lipid level and treatment group. The Last Observation Carry Forward (LOCF) approach was applied for missing data or data collected after modifying lipid-lowering

therapy. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had a measurement at Baseline and at the time point assessed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	326	318		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	91.10 (± 28.61)	91.76 (± 30.36)		
Change from Baseline	-4.51 (± 20.64)	9.92 (± 27.31)		

Statistical analyses

Statistical analysis title	Mean Change from BL in Fasting LDL-C at Week 48
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	644
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment Difference (mg/dL)
Point estimate	-14.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.15
upper limit	-11.06

Secondary: Change from Baseline in Mean CD4+ T-cell Count at Week 96

End point title	Change from Baseline in Mean CD4+ T-cell Count at Week 96

End point description:

CD4+ T-cell counts were quantified by a central laboratory using a commercially available assay. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had data for the outcome measure. Baseline values were carried forward for participants who discontinued therapy due to lack of efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	342	327		
Units: Cells/mm^3				
arithmetic mean (confidence interval 95%)	224.1 (200.8 to 247.4)	206.7 (184.9 to 228.5)		

Statistical analyses

Statistical analysis title	Chg from BL in Mean CD4+ T-cell Count at Wk 96
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean treatment difference
Point estimate	17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	49.3

Secondary: Mean Change from Baseline in Fasting Non-High Density Lipoprotein Cholesterol (non-HDL-C) at Week 48

End point title	Mean Change from Baseline in Fasting Non-High Density Lipoprotein Cholesterol (non-HDL-C) at Week 48

End point description:

Serum non-HDL-C was determined after an overnight fast. Change from Baseline was analyzed using ANCOVA models with terms for Baseline lipid level and treatment group. The LOCF approach was applied for missing data or data collected after modifying lipid-lowering therapy. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had a measurement at Baseline and at the time point assessed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	329	325		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	113.34 (± 34.25)	114.44 (± 35.01)		
Change from Baseline	-5.30 (± 23.28)	13.75 (± 31.08)		

Statistical analyses

Statistical analysis title	Mean Change from BL in Fasting non-HDL-C at Wk 48
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	654
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment Difference (mg/dL)
Point estimate	-19.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.33
upper limit	-15.35

Secondary: Mean Change from Baseline in Fasting High Density Lipoprotein Cholesterol (HDL-C) at Week 48

End point title	Mean Change from Baseline in Fasting High Density Lipoprotein Cholesterol (HDL-C) at Week 48

End point description:

Serum HDL-C was determined after an overnight fast. Change from Baseline was analyzed using ANCOVA models with terms for Baseline lipid level and treatment group. The LOCF approach was applied for missing data or data collected after modifying lipid-lowering therapy. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had a measurement at Baseline and at the time point assessed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	329	325		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	43.58 (± 12.99)	43.27 (± 13.96)		
Change from Baseline	3.94 (± 10.66)	4.15 (± 11.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Fasting Total Cholesterol at Week 48

End point title	Mean Change from Baseline in Fasting Total Cholesterol at Week 48

End point description:

Serum total cholesterol was determined after an overnight fast. Change from Baseline was analyzed using ANCOVA models with terms for Baseline lipid level and treatment group. The LOCF approach was applied for missing data or data collected after modifying lipid-lowering therapy. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had a measurement at Baseline and at the time point assessed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	329	325		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	156.92 (± 35.82)	157.71 (± 37.34)		
Change from Baseline	-1.37 (± 25.47)	17.90 (± 33.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Any Adverse Event

End point title	Percentage of Participants with Any Adverse Event

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a study participant and which does not necessarily have to have a causal relationship to treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the study treatment or protocol-specified procedure, whether or not considered related to study treatment or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study treatment is also an AE. The percentage of participants with any AE was assessed. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 98 weeks

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of participants				
number (not applicable)	84.6	82.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Fasting Triglyceride at Week 48

End point title	Mean Change from Baseline in Fasting Triglyceride at Week 48

End point description:

Serum triglyceride was determined after an overnight fast. Change from Baseline was analyzed using ANCOVA models with terms for Baseline lipid level and treatment group. The LOCF approach was applied for missing data or data collected after modifying lipid-lowering therapy. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had a measurement at Baseline and at the time point assessed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	329	325		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	111.16 (± 75.31)	117.02 (± 97.30)		
Change from Baseline	-3.14 (± 68.81)	21.97 (± 92.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Any Serious Adverse Event

End point title	Percentage of Participants with Any Serious Adverse Event

End point description:

A serious adverse event is an AE that results in death, is life threatening, results in persistent or significant disability or incapacity, results in or prolongs a hospitalization, is a congenital anomaly or birth defect, is a cancer, is associated with an overdose, or is another important medical event. The percentage of participants with any SAE was assessed. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 98 weeks

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of participants				
number (not applicable)	7.0	8.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Any Drug-related Adverse Event

End point title	Percentage of Participants with Any Drug-related Adverse Event

End point description:

The investigator was to determine if an AE had a reasonable possibility of a relationship to the study drug. The percentage of participants with any drug-related AE was assessed. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 98 weeks

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of participants				
number (not applicable)	32.1	32.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Any Drug-related Serious Adverse Event

End point title	Percentage of Participants with Any Drug-related Serious Adverse Event

End point description:

The percentage of participants with any drug-related SAE was assessed. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 98 weeks

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of participants				
number (not applicable)	0.3	0.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Discontinued Study Treatment Due to an Adverse Event

End point title	Percentage of Participants Who Discontinued Study Treatment Due to an Adverse Event

End point description:

The percentage of participants who discontinued study treatment due to an AE was assessed. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 96 weeks

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of Participants				
number (not applicable)	1.6	3.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Plasma HIV-1 RNA <40 Copies/mL at Week 48

End point title	Percentage of Participants Achieving Plasma HIV-1 RNA <40 Copies/mL at Week 48

End point description:

The percentage of participants in each arm achieving HIV-1 RNA levels <40 copies/mL at Week 48 was determined. Plasma HIV-1 RNA levels were quantified with the Abbott RealTime HIV-1 Assay. Data were handled according to the US Food and Drug Administration (FDA) "snapshot" approach and all missing data were considered treatment failures, regardless of the reason. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 48

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	383	383		
Units: Percentage of participants				
number (not applicable)	83.3	79.1		

Statistical analyses

Statistical analysis title	% Achieving PL HIV-1 RNA <40 Copies/mL at Wk 48
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg

Number of subjects included in analysis	766
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	4.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.404
upper limit	9.743

Secondary: Percentage of Participants Achieving Plasma HIV-1 RNA <40 Copies/mL at Week 96

End point title	Percentage of Participants Achieving Plasma HIV-1 RNA <40 Copies/mL at Week 96

End point description:

The percentage of participants in each arm achieving HIV-1 RNA levels <40 copies/mL at Week 96 was determined. Plasma HIV-1 RNA levels were quantified with the Abbott RealTime HIV-1 Assay. Data were handled according to the US Food and Drug Administration (FDA) "snapshot" approach and all missing data were considered treatment failures, regardless of the reason. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study drug and had data for the outcome measure. Participants with missing HIV-1 RNA due to an Abbott RealTime manufacturing agent recall were excluded from the analysis.

End point type	Secondary

End point timeframe:

Week 96

End point values	Doravirine 100 mg	Daurunavir 800 mg + Ritonavir 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	379	376		
Units: Percentage of participants				
number (not applicable)	72.0	64.4		

Statistical analyses

Statistical analysis title	% Achieving PL HIV-1 RNA <40 Copies/mL at Wk 96
Comparison groups	Doravirine 100 mg v Daurunavir 800 mg + Ritonavir 100 mg
Number of subjects included in analysis	755
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	7.606

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	14.232

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 386

Adverse event reporting additional description:

The analysis population for Deaths (all causes) included all randomized participants. The analysis population for Serious and Non Serious Adverse Events included all participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg

Reporting group description:

Double-blind Darunavir 800 mg and Ritonavir 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Reporting group title	Doravirine 100 mg

Reporting group description:

Double-blind Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/KIVEXA™ administered p.o. q.d. for 96 weeks in the Base Study. Eligible participants continued in Study Extension 1 with open-label Doravirine 100 mg administered p.o. q.d. + investigator-selected TRUVADA™ or EPZICOM™/ KIVEXA™ administered p.o. q.d. for an additional 96 weeks. Eligible participants continued to receive the Doravirine regimen in Study Extension 2 for an additional 96 weeks, and in Study Extension 3 for an additional 96 weeks.

Serious adverse events	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg	Doravirine 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 383 (12.79%)	45 / 383 (11.75%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiosarcoma			

subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			

subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral artery aneurysm			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Post abortion haemorrhage			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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			
Death			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			

subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Drug abuser			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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			
Prostatitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (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			
Acute pulmonary oedema			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stridor			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced mood disorder			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective disorder depressive type			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure to toxic agent			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ligament rupture			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal injury			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 383 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Supraventricular tachycardia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bell's palsy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osmotic demyelination syndrome			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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			
Neutropenia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal skin tags			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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			
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (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 / 383 (0.00%)	1 / 383 (0.26%)	
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	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute hepatitis C			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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 / 383 (0.26%)	0 / 383 (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	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 383 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis C			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis shigella			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes oesophagitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratouveitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosyphilis			

subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis tuberculous			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal disease			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis of central nervous system			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
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 / 383 (0.26%)	0 / 383 (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	Daurunavir 800 mg + Ritonavir 100 mg Doravirine 100 mg	Doravirine 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 383 (64.49%)	264 / 383 (68.93%)	
Nervous system disorders			
Headache			
subjects affected / exposed	59 / 383 (15.40%)	63 / 383 (16.45%)	
occurrences (all)	92	106	
Dizziness			
subjects affected / exposed	24 / 383 (6.27%)	25 / 383 (6.53%)	
occurrences (all)	28	28	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 383 (2.61%)	21 / 383 (5.48%)	
occurrences (all)	10	21	
Fatigue			
subjects affected / exposed	28 / 383 (7.31%)	38 / 383 (9.92%)	
occurrences (all)	30	40	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	54 / 383 (14.10%)	52 / 383 (13.58%)	
occurrences (all)	64	65	
Diarrhoea			
subjects affected / exposed	100 / 383 (26.11%)	72 / 383 (18.80%)	
occurrences (all)	136	87	
Abdominal pain			
subjects affected / exposed	20 / 383 (5.22%)	20 / 383 (5.22%)	
occurrences (all)	25	22	
Abdominal pain upper			

subjects affected / exposed	15 / 383 (3.92%)	27 / 383 (7.05%)	
occurrences (all)	18	30	
Vomiting			
subjects affected / exposed	12 / 383 (3.13%)	20 / 383 (5.22%)	
occurrences (all)	14	32	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 383 (3.66%)	38 / 383 (9.92%)	
occurrences (all)	15	48	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	23 / 383 (6.01%)	27 / 383 (7.05%)	
occurrences (all)	27	27	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 383 (5.74%)	26 / 383 (6.79%)	
occurrences (all)	27	29	
Back pain			
subjects affected / exposed	13 / 383 (3.39%)	37 / 383 (9.66%)	
occurrences (all)	16	45	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	23 / 383 (6.01%)	22 / 383 (5.74%)	
occurrences (all)	28	25	
Bronchitis			
subjects affected / exposed	37 / 383 (9.66%)	31 / 383 (8.09%)	
occurrences (all)	42	43	
Influenza			
subjects affected / exposed	16 / 383 (4.18%)	24 / 383 (6.27%)	
occurrences (all)	20	29	
Upper respiratory tract infection			
subjects affected / exposed	40 / 383 (10.44%)	64 / 383 (16.71%)	
occurrences (all)	59	115	
Syphilis			
subjects affected / exposed	39 / 383 (10.18%)	29 / 383 (7.57%)	
occurrences (all)	47	39	

Nasopharyngitis subjects affected / exposed occurrences (all)	61 / 383 (15.93%) 102	61 / 383 (15.93%) 110	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2015	Amendment 01: The primary reasons for this protocol amendment were revisions to the Objectives and Hypotheses, Efficacy Endpoints, Statistical Analysis Plan, Subject Inclusion Criteria, Subject Withdrawal/Discontinuation Criteria, and Timing of Dose Administration.
12 February 2015	Amendment 02: The primary reasons for this protocol amendment were revisions to the Objectives and Hypotheses, Efficacy Endpoints, Statistical Analysis Plan, Subject Inclusion Criteria, Subject Withdrawal/Discontinuation Criteria, and Timing of Dose.
23 July 2015	Amendment 03: The primary reasons for this protocol amendment were revisions to the Objectives and Hypotheses, Efficacy Endpoints, Statistical Analysis Plan, Subject Inclusion Criteria, Subject Exclusion Criteria, Subject Withdrawal/Discontinuation Criteria, Timing of Dose Administration, and Concomitant Medications/Vaccinations (Allowed & Prohibited).
02 December 2016	Amendment 05: The primary reasons for this protocol amendment were revisions to the Trial Summary, Trial Design, Trial Diagram, Exploratory Objectives, Rationale for Endpoints, Rationale for Study Extension, Subject Inclusion Criteria, Trial Treatments, Dose Modification/Interruption/Discontinuation, Timing of Dose Administration, Trial Blinding/Masking, Concomitant Medications, Subject Withdrawal/Discontinuation Criteria, Trial Flow Chart, Inclusion/Exclusion Criteria, Adverse Events, Laboratory Procedures/Assessments, Blinding/Unblinding, Treatment Visits in Base Study (Visit 2 to Visit 13), Treatment Visits in Study Extension (Visit 14 to Visit 20), Post-Trial, Statistical Analysis Plan, Responsibility for Analyses/In-House Blinding, Statistical Methods, Compliance (Medication Adherence), and Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types.
12 December 2016	Amendment 04 : The primary reasons for this protocol amendment were revisions to reflect an amended trial design, which added an open-label extension in which patients received active MK-1439 in combination with NRTI, after completion of the 96-week, double-blind period (base study).
09 March 2017	Amendment 06: The primary reasons for this protocol amendment were revisions to the Trial Summary, Trial Design, Trial Diagram, Exploratory Objectives, Rationale for Endpoints, Rationale for Study Extension, Subject Inclusion Criteria, Trial Treatments, Dose Modification/Interruption/Discontinuation, Timing of Dose Administration, Trial Blinding/Masking, Concomitant Medications, Subject Withdrawal/Discontinuation Criteria, Trial Flow Chart, Inclusion/Exclusion Criteria, Adverse Events, Laboratory Procedures/Assessments, Blinding/Unblinding, Treatment Visits in Base Study (Visit 2 to Visit 13), Treatment Visits in Study Extension (Visit 14 to Visit 20), Post-Trial, Statistical Analysis Plan, Responsibility for Analyses/In-House Blinding, Statistical Methods, Compliance (Medication Adherence), Approximate Blood/Tissue Volumes, Drawn/Collected by Trial Visit and by Sample Types, Rationale for the Trial and Selected Subject Population, and Subject Inclusion Criteria.

30 August 2018	Amendment 08: The primary reasons for this protocol amendment were revisions to the Trial Design, Trial Diagram, Study Extension, Efficacy Endpoints, Safety Endpoints, Rationale for Study Extensions, Trial Treatments, Dose Modification/Interruption/Discontinuation, Concomitant Medications, Subject Withdrawal/Discontinuation Criteria, Trial Flow Chart, Inclusion/Exclusion Criteria, Trial Compliance (Medication/Diet/Activity/Other), Adverse Events, Serum/Urine Pregnancy Test Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis), Virology Test, Viral Resistance Testing, CD4 Cell Counts, Blinding/Unblinding, Treatment Visits in Base Study, Treatment Visits in Study Extension 1, Post-Trial, Assessing and Recording Adverse Events, Data Monitoring Committee, Statistical Analysis Plan, Responsibility for Analyses/In-House Blinding, Analysis Endpoints, Statistical Methods, Statistical Methods for Efficacy Analysis, Compliance (Medication Adherence), Packaging and Labeling Information, and Week 100 Through Post-Study 14-Day Follow-up (Study Extension 1).
14 January 2019	Amendment 10: The primary reasons for this protocol amendment were revisions to the Trial Summary, Duration of Participation, Trial Design, Trial Flowchart, Subject Withdrawal/Discontinuation Criteria, Treatment Visits in Study Extension, and Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types in Study Extension.
14 February 2019	Amendment 07: The primary reasons for this protocol amendment were revisions to the Trial Summary, Trial Design, Trial Diagram, Study Extension, Efficacy Endpoints, Safety Endpoints, Rationale for Study Extensions, Subject Inclusion Criteria, Trial Treatments, Dose Modification/Interruption/Discontinuation, Concomitant Medications, Subject Withdrawal/Discontinuation Criteria, Trial Flow Chart, Inclusion/Exclusion Criteria, Trial Compliance, Adverse Events, Serum/Urine Pregnancy Test, Laboratory Safety Evaluations, Virology Test, Viral Resistance Testing, CD4 Cell Counts, Blinding/Unblinding, Treatment Visits in Base Study, Treatment Visits in Study Extension 1, Post-Trial, Assessing and Recording Adverse Events, Data Monitoring Committee, Statistical Analysis Plan, Responsibility for Analyses/In-House Blinding, Analysis Endpoints, Statistical Methods, Statistical Methods for Efficacy Analysis, Compliance (Medication Adherence), Packaging and Labeling Information, Week 100 Through Post-Study 14-Day Follow-up (Study Extension 1).
21 March 2019	Amendment 09: The primary reasons for this protocol amendment were revisions to the Trial Summary, Trial Design, Trial Diagram, Study Extension, Efficacy Endpoints, Safety Endpoints, Rationale for Study Extensions, Subject Inclusion Criteria, Trial Treatments, Dose Modification/Interruption/Discontinuation, Concomitant Medications, Subject Withdrawal/Discontinuation Criteria, Trial Flow Chart, Inclusion/Exclusion Criteria, Trial Compliance, Medication/Diet/Activity/Other), Adverse Events, Serum/Urine Pregnancy Test, Laboratory Safety Evaluations, Virology Test, Viral Resistance Testing, CD4 Cell Counts, Blinding/Unblinding, Treatment Visits in Base Study, Treatment Visits in Study Extension 1, Post-Trial, Assessing and Recording Adverse Events, Data Monitoring Committee, Statistical Analysis Plan, Responsibility for Analyses/In-House Blinding, Analysis Endpoints, Statistical Methods, Statistical Methods for Efficacy Analysis, Compliance (Medication Adherence), Packaging and Labeling Information, and Week 100 Through Post-Study 14-Day Follow-up (Study Extension 1).
15 December 2020	Amendment 11: The primary reasons for this protocol amendment were revisions to the Trial Summary, Trial Design, Trial Diagram, Safety Endpoints, Rationale for Study Extensions, Subject Withdrawal/Discontinuation Criteria, Trial Flow Chart, Inclusion/Exclusion Criteria, Trial Compliance (Medication/Diet/Activity/Other), Withdrawal/Discontinuation, Visit Requirements, Assessing and Recording Adverse Events, Statistical Analysis Plan, Responsibility for Analyses/In-House Blinding, and Statistical Methods.
16 January 2023	Amendment 12: The primary reasons for this protocol amendment were to update the Sponsor name and address.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported