

**Clinical trial results:****AN OPEN-LABEL, MULTICENTER, MULTIPLE-DOSE PHARMACOKINETIC AND 48-WEEK SAFETY AND EFFICACY TRIAL OF MARAVIROC IN COMBINATION WITH OPTIMIZED BACKGROUND THERAPY FOR THE TREATMENT OF ANTIRETROVIRAL-EXPERIENCED CCR5-TROPIC HIV-1 INFECTED CHILDREN 2-18 YEARS OF AGE****Summary**

EudraCT number	2008-006873-33
Trial protocol	ES PT IT GB FR Outside EU/EEA
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	04 October 2019
First version publication date	14 April 2016
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	A4001031
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00791700
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	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000020-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	11 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This study aimed to:

Primary objectives:

- determine the PK profile(s) and dosing schedule(s) for MVC in treatment experienced HIV infected children and adolescents on different background therapies;
- determine the safety and tolerability of MVC in HIV infected children and adolescents.

Secondary objectives:

- describe the efficacy of multiple dose administration of MVC in treatment experienced children infected with R5 HIV 1;
- describe tropism changes over time

Protection of trial subjects:

This study was designed and monitored in accordance with Pfizer standard operating procedures (SOPs), until transition to the Contract Research Organization (CRO) PAREXEL in November 2012, after which the study was monitored in accordance with CRO SOPs. Both Pfizer and CRO SOPs complied with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki as amended by legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008). In addition, the study was conducted in accordance with the CSP, the International Conference on Harmonization guideline on GCP, and applicable local regulatory requirements and laws.

Background therapy:

Optimized background treatment (OBT), consisting of 3 to 5 commercially available Anti-retroviral (ARV) agents were selected by the investigator and approved by Pfizer, on the basis of resistance testing, treatment history and safety considerations. Subjects with toxicity due to drugs in the OBT regimen were able to substitute a drug of the same class during the study in consultation with the medical monitor. All concomitant medications were recorded on the CRF. Although no other forms of therapy for the treatment of HIV infection will be allowed while on study medication, IVIG for the treatment of HIV infection is allowed. ARV agents comprising the OBT regimen were taken according to the manufacturer product labeling or local guidelines. Dose adjustments to Maraviroc (MVC) were made in subjects taking concomitant medications that significantly inhibit and/or induce CYP3A4. This is because MVC is a substrate for CYP3A4. Medications such as analgesics, antiinflammatory agents, antibiotics, and nutritional supplements other than those contraindicated (list below), could be used as needed. Contraindicated medications included but not limited to were immunomodulators (except interferon or IVIG), grapefruit or grapefruit related citrus fruits (eg, Seville oranges, pomelos) and St.John's Wort or other herbal therapies. The use of rifampin for the treatment mycobacterial infection for subjects in Stage 2 was allowed on a case-by-case basis with the approval of the study team. Rifampin was not allowed for subjects in Stage 1. Co-administration of isoniazid was allowed on an individual basis upon discussion with and approval of the study team.

Evidence for comparator: -

Actual start date of recruitment	22 April 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	South Africa: 62
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	103
EEA total number of subjects	11

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)	61
Adolescents (12-17 years)	42
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This open-label, multicenter, multiple dose pharmacokinetic, safety and efficacy study enrolled 103 subjects at 24 sites in 8 countries. Data reported in this result summary is the 5 year safety update.

Pre-assignment

Screening details:

Criteria such as the following were considered: HIV-1 infected treatment-experienced children and adolescents who were failing current ARV therapy or have failed their most recent ARV regimen, defined by plasma HIV-1 RNA \geq 1000 copies/mL, infected with only R5 HIV-1, and have ARV experience/intolerance of 6 months with at least 2 ARV drug classes.

Period 1

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

Blinding implementation details:

Open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

\geq 2 - <6 years of age, MVC liquid formulation

Arm type	Experimental
Investigational medicinal product name	Maraviroc
Investigational medicinal product code	UK-427,857
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

MVC liquid formulation (20 mg/ml)

Arm title	Cohort 2
------------------	----------

Arm description:

\geq 6 - <12 years of age, MVC tablet formulation

Arm type	Experimental
Investigational medicinal product name	Maraviroc
Investigational medicinal product code	UK-427,857
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MVC tablet formulation (25 mg, 75 mg, 150 mg)

Arm title	Cohort 3
------------------	----------

Arm description:

\geq 6 - <12 years of age, MVC liquid formulation

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Maraviroc
Investigational medicinal product code	UK-427,857
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

MVC liquid formulation (20 mg/ml)

Arm title	Cohort 4
------------------	----------

Arm description:

>=12 - <18 years of age, MVC tablet formulation

Arm type	Experimental
Investigational medicinal product name	Maraviroc
Investigational medicinal product code	UK-427,857
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MVC tablet formulation (25 mg, 75 mg, 150 mg)

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	16	31	13
Completed	10	20	7
Not completed	6	11	6
Adverse Event	-	-	1
Death	-	-	-
No longer willing to participate in study	1	1	-
Non-compliance with study treatment	-	2	-
Withdrawn due to pregnancy	-	-	-
Unspecified	-	1	-
Lost to follow-up	4	3	4
Insufficient clinical response	1	4	1

Number of subjects in period 1	Cohort 4
Started	43
Completed	13
Not completed	30
Adverse Event	1
Death	1
No longer willing to participate in study	8
Non-compliance with study treatment	4
Withdrawn due to pregnancy	1

Unspecified	1
Lost to follow-up	6
Insufficient clinical response	8

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
Reporting group description: >=2 - <6 years of age, MVC liquid formulation	
Reporting group title	Cohort 2
Reporting group description: >=6 - <12 years of age, MVC tablet formulation	
Reporting group title	Cohort 3
Reporting group description: >=6 - <12 years of age, MVC liquid formulation	
Reporting group title	Cohort 4
Reporting group description: >=12 - <18 years of age, MVC tablet formulation	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	16	31	13
Age categorical Units: Subjects			
Children (2-11 years)	16	31	13
Adolescents (12-17 years)	0	0	0
Age Continuous Units: years			
arithmetic mean	3.4	9.1	8.9
standard deviation	± 0.9	± 1.7	± 2.0
Gender, Male/Female Units: participants			
Female	5	16	6
Male	11	15	7

Reporting group values	Cohort 4	Total	
Number of subjects	43	103	
Age categorical Units: Subjects			
Children (2-11 years)	1	61	
Adolescents (12-17 years)	42	42	
Age Continuous Units: years			
arithmetic mean	14.0	-	
standard deviation	± 1.6	-	
Gender, Male/Female Units: participants			
Female	27	54	
Male	16	49	

Subject analysis sets

Subject analysis set title	Response
Subject analysis set type	Full analysis
Subject analysis set description: Subjects with plasma HIV-1 RNA <48 copies/mL at Week 48 using Missing, Switch, Discontinuation'=Failure (MSDF) algorithm.	
Subject analysis set title	PDVF
Subject analysis set type	Full analysis
Subject analysis set description: Subjects with protocol-defined virologic failure	
Subject analysis set title	Other Failure/Remainder
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who discontinued due to other reasons.	
Subject analysis set title	Cohort 1 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=2 - <6 years of age, MVC liquid formulation	
Subject analysis set title	Cohort 1 (Grade 4)
Subject analysis set type	Safety analysis
Subject analysis set description: >=2 - <6 years of age, MVC liquid formulation	
Subject analysis set title	Cohort 2 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6 - <12 years of age, MVC tablet formulation	
Subject analysis set title	Cohort 2 (Grade 4)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6 - <12 years of age, MVC tablet formulation	
Subject analysis set title	Cohort 3 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6 - <12 years of age, MVC liquid formulation	
Subject analysis set title	Cohort 3 (Grade 4)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6- <12years of age, MVC liquid formulation	
Subject analysis set title	Cohort 4 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=12 - <18 years of age, MVC tablet formulation	
Subject analysis set title	Cohort 4 (Grade 4)
Subject analysis set type	Safety analysis
Subject analysis set description: >=12 - <18 years of age, MVC tablet formulation	

Reporting group values	Response	PDVF	Other Failure/Remainder
Number of subjects	49	23	31

Age categorical Units: Subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Age Continuous Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female Units: participants			
Female	0	0	0
Male	0	0	0

Reporting group values	Cohort 1 (Grade 3)	Cohort 1 (Grade 4)	Cohort 2 (Grade 3)
Number of subjects	16	16	31
Age categorical Units: Subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Age Continuous Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female Units: participants			
Female	0	0	0
Male	0	0	0

Reporting group values	Cohort 2 (Grade 4)	Cohort 3 (Grade 3)	Cohort 3 (Grade 4)
Number of subjects	31	13	13
Age categorical Units: Subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Age Continuous Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female Units: participants			
Female	0	0	0
Male	0	0	0

Reporting group values	Cohort 4 (Grade 3)	Cohort 4 (Grade 4)	
Number of subjects	43	43	
Age categorical Units: Subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	

Age Continuous			
Units: years			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Gender, Male/Female			
Units: participants			
Female	0	0	
Male	0	0	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: >=2 - <6 years of age, MVC liquid formulation	
Reporting group title	Cohort 2
Reporting group description: >=6 - <12 years of age, MVC tablet formulation	
Reporting group title	Cohort 3
Reporting group description: >=6 - <12 years of age, MVC liquid formulation	
Reporting group title	Cohort 4
Reporting group description: >=12 - <18 years of age, MVC tablet formulation	
Subject analysis set title	Response
Subject analysis set type	Full analysis
Subject analysis set description: Subjects with plasma HIV-1 RNA <48 copies/mL at Week 48 using Missing, Switch, Discontinuation'=Failure (MSDF) algorithm.	
Subject analysis set title	PDVF
Subject analysis set type	Full analysis
Subject analysis set description: Subjects with protocol-defined virologic failure	
Subject analysis set title	Other Failure/Remainder
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who discontinued due to other reasons.	
Subject analysis set title	Cohort 1 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=2 - <6 years of age, MVC liquid formulation	
Subject analysis set title	Cohort 1 (Grade 4)
Subject analysis set type	Safety analysis
Subject analysis set description: >=2 - <6 years of age, MVC liquid formulation	
Subject analysis set title	Cohort 2 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6 - <12 years of age, MVC tablet formulation	
Subject analysis set title	Cohort 2 (Grade 4)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6 - <12 years of age, MVC tablet formulation	
Subject analysis set title	Cohort 3 (Grade 3)
Subject analysis set type	Safety analysis
Subject analysis set description: >=6 - <12 years of age, MVC liquid formulation	
Subject analysis set title	Cohort 3 (Grade 4)
Subject analysis set type	Safety analysis

Subject analysis set description:

>=6- <12years of age, MVC liquid formulation

Subject analysis set title	Cohort 4 (Grade 3)
Subject analysis set type	Safety analysis

Subject analysis set description:

>=12 - <18 years of age, MVC tablet formulation

Subject analysis set title	Cohort 4 (Grade 4)
Subject analysis set type	Safety analysis

Subject analysis set description:

>=12 - <18 years of age, MVC tablet formulation

Primary: Pharmacokinetic (PK) Parameters for subjects with data in Stage 1 enrolled in Stage 2 – Week 2 and Week 48

End point title	Pharmacokinetic (PK) Parameters for subjects with data in Stage 1 enrolled in Stage 2 – Week 2 and Week 48 ^[1]
-----------------	---

End point description:

A PK analysis was performed using PK data from subjects that participated in Stage 1 (PK Populations 2 and 3) where intensive MVC PK data were available at Week 2. The primary aim of this analysis was to describe and summarize MVC PK parameters at Week 2 and Week 48 by cohort and OBT group. Geometric Coefficient of Variation is defined as the geometric standard deviation to the power of the reciprocal of the geometric mean. PK analysis was also performed for Population 2 (subset of APS 1) consisting of all Stage 1 subjects who had a Week 2 full PK profile; and for Population 3 (subset of APS 1) consisting of all Stage 1 subjects who had an approved dose for Stage 2 / met the PK target. Number of Subjects Analyzed signifies the number of subjects analyzed for PK. n= number of subjects analyzed at individual time points for this outcome measure.

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

End point timeframe:

Week 2 and Week 48 (0, 1, 2, 4, 6, 8, 12 hours post-dose)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were done.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	12	42
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cavg-Week2(n=12, 11, 10, 17)	237.34 (± 63)	260.65 (± 43)	264.45 (± 62)	239.85 (± 67)
Cavg-Week 48(n=9, 8, 8, 12)	163.73 (± 146)	289.69 (± 50)	168.62 (± 117)	199.12 (± 78)
Cmax-Week2 (n=12, 11, 10, 17)	581.47 (± 69)	546.80 (± 51)	444.37 (± 61)	530.80 (± 62)
Cmax-Week 48(n=9, 8, 8, 12)	334.68 (± 156)	593.68 (± 25)	284.96 (± 128)	423.32 (± 48)
Cmin-Week2(n=12, 11, 10, 17)	18.97 (± 202208)	100.02 (± 39)	115.84 (± 90)	56.17 (± 145)
Cmin-Week 48(n=9, 8, 8, 12)	48.11 (± 180)	82.21 (± 120)	60.03 (± 245)	66.51 (± 140)

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameters for Stage 1 subjects Enrolled in Stage 2 – Week 2 and Week 48 Results for Stage 2 doses - AUCtau (Area under the curve at steady state)

End point title	PK Parameters for Stage 1 subjects Enrolled in Stage 2 – Week 2 and Week 48 Results for Stage 2 doses - AUCtau (Area under the curve at steady state) ^[2]
-----------------	--

End point description:

A PK analysis was performed using PK data from participants that participated in Stage 1 (PK Populations 2 and 3) where intensive MVC PK data were available at Week 2. The primary aim of this analysis was to describe and summarize MVC PK parameters (AUCtau) at Week 2 and Week 48 by cohort and OBT group. Correlations between MVC PK and efficacy as well as compliance were also assessed. PK analysis was also performed for Population 2 (subset of APS 1) consisting of all Stage 1 participants who had a Week 2 full PK profile; and for Population 3 (subset of APS 1) consisting of all Stage 1 participants who had an approved dose for Stage 2 / met the PK target. Number of Subjects Analyzed signifies the number of subjects analyzed for PK. n= number of subjects analyzed at individual time points for this outcome measure.

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

End point timeframe:

Week 2 and Week 48 (0, 1, 2, 4, 6, 8, 12 hours post-dose)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were done.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	12	42
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUCtau - Week 2 (n=12, 11, 10, 17)	2848.1 (± 63)	3127.7 (± 43)	3173.4 (± 62)	2878.2 (± 67)
AUCtau - Week 48 (n=9, 8, 8, 12)	1964.7 (± 146)	3476.3 (± 50)	2023.5 (± 117)	2389.4 (± 78)

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameters for Stage 1 subjects Enrolled in Stage 2 – Week 2 and Week 48 Results for Stage 2 doses - Tmax (Time at maximum concentration)

End point title	PK Parameters for Stage 1 subjects Enrolled in Stage 2 – Week 2 and Week 48 Results for Stage 2 doses - Tmax (Time at maximum concentration) ^[3]
-----------------	---

End point description:

A PK analysis was performed using PK data from subjects that participated in Stage 1 (PK Populations 2 and 3) where intensive MVC PK data were available at Week 2. The primary aim of this analysis was to describe and summarize MVC PK parameters (Tmax) at Week 2 and Week 48 by cohort and OBT group. Correlations between MVC PK and efficacy as well as compliance were also assessed. PK analysis was also performed for Population 2 (subset of APS 1) consisting of all Stage 1 subjects who had a Week 2 full PK profile; and for Population 3 (subset of APS 1) consisting of all Stage 1 subjects who had an approved dose for Stage 2 / met the PK target. Number of Subjects Analyzed signifies the number of subjects analyzed for PK. n= number of subjects analyzed at individual time points for this outcome measure.

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

End point timeframe:

Week 2 and Week 48 (0, 1, 2, 4, 6, 8, 12 hours post-dose)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were done.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	12	42
Units: hour				
median (full range (min-max))				
Tmax - Week 2 (n=12, 11, 10, 17)	2.000 (0.97 to 6.00)	4.000 (0.75 to 6.00)	2.000 (1.00 to 4.00)	2.000 (1.00 to 4.00)
Tmax - Week 48 (n=9, 8, 8, 12)	2.000 (0.00 to 6.03)	2.000 (1.00 to 8.00)	3.000 (0.00 to 6.00)	2.000 (1.00 to 4.00)

Statistical analyses

No statistical analyses for this end point

Primary: Incidence and Severity of Grade 3 and Grade 4 Treatment-Emergent Adverse Events (All Causality)

End point title	Incidence and Severity of Grade 3 and Grade 4 Treatment-Emergent Adverse Events (All Causality) ^[4]
-----------------	--

End point description:

Safety analysis was performed on all subjects who received at least 1 dose of study drug. It was assessed by spontaneous reports, physical examination and laboratory test results in all subjects who received at least 1 dose of study drug. The investigator used the Division of AIDS (DAIDS) version 4 Table for Grading the Severity of Adult and Pediatric AEs. MCT disorders= Musculoskeletal and Connective Tissue Disorder.

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

End point timeframe:

Baseline up to 5 years

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were done.

End point values	Cohort 1 (Grade 3)	Cohort 1 (Grade 4)	Cohort 2 (Grade 3)	Cohort 2 (Grade 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	16	31	31
Units: Number of events				
Gastrointestinal disorders - Vomiting	1	0	1	0
Hepat. disorders - Drug-induced liver injury	0	0	0	0
Infections and infestations - H1N1 influenza	0	0	0	0
Infections and infestations - Pneumonia	0	0	0	0
Investigations - Lipase increased	0	1	0	0
Psychiatric disorder - Bipolar disorder	0	0	1	0
Gastrointestinal disorders - Gastritis	0	0	1	0
Investigations - Hepatic enzyme abnormal	0	0	1	0

Investigations - Transaminases increased	0	0	1	0
Pyschiatric disorder - Aggression	0	0	1	0
Blood and lymphatic system disorders - Anaemia	0	0	0	0
Infections and infestations - Meningitis	0	0	0	0
Otitis media	0	0	1	0

End point values	Cohort 3 (Grade 3)	Cohort 3 (Grade 4)	Cohort 4 (Grade 3)	Cohort 4 (Grade 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	13	43	43
Units: Number of events				
Gastrointestinal disorders - Vomiting	0	0	0	0
Hepat. disorders - Drug-induced liver injury	0	0	0	1
Infections and infestations - H1N1 influenza	0	0	1	0
Infections and infestations - Pneumonia	1	0	1	0
Investigations - Lipase increased	0	0	0	0
Pyschiatric disorder - Bipolar disorder	0	0	0	0
Gastrointestinal disorders - Gastritis	0	0	0	0
Investigations - Hepatic enzyme abnormal	0	0	0	0
Investigations - Transaminases increased	0	0	0	0
Pyschiatric disorder - Aggression	0	0	0	0
Blood and lymphatic system disorders - Anaemia	0	0	1	0
Infections and infestations - Meningitis	0	0	0	1
Otitis media	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Treatment discontinuation secondary to Serious Adverse Event (SAE) related to study drug

End point title	Treatment discontinuation secondary to Serious Adverse Event (SAE) related to study drug ^[5]
-----------------	---

End point description:

The primary reason for a subject discontinuing from study drug or the clinical study was recorded in the source documents as well as the case report form. A discontinuation had to be reported immediately to the study medical monitor or his/her designated representative if it was due to an SAE. Safety analysis was performed on all subjects who received at least 1 dose of study drug. In this study, there was no treatment discontinuation secondary to Serious Adverse Event (SAE) related to study drug.

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

End point timeframe:

Baseline up to 5 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were done.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: subejcts	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with HIV1 RNA <400 copies/mL through Week 48 (MSDF)

End point title	Percentage of subjects with HIV1 RNA <400 copies/mL through Week 48 (MSDF)
-----------------	--

End point description:

The proportion of subjects who achieved HIV-1 RNA <400 copies/mL at week 24 or 48 was assessed according to Food and Drug Administration's (FDA's) MSDF Snapshot algorithm. The algorithm uses the plasma HIV-1 RNA in the Week 24 or 48 visit window, follows the "virology-first principle" and considers a subject who has a missing plasma HIV-1 RNA, or switches to prohibited ARV regimen or discontinues from the study or study drug for any reason, or dies, as a failure. The percentage of subjects is reported below.

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

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: percentage of subjects				
number (not applicable)				
Week 24	68.8	90.3	69.2	62.8
Week 48	75.0	77.4	69.2	51.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with HIV1 RNA <48 copies/mL through Week 48 (MSDF)

End point title	Percentage of subjects with HIV1 RNA <48 copies/mL through Week 48 (MSDF)
-----------------	---

End point description:

The proportion of subjects who achieved HIV-1 RNA <48 copies/mL at week 24 or 48 was assessed according to Food and Drug Administration's (FDA's) MSDF Snapshot algorithm. The algorithm uses the plasma HIV-1 RNA in the Week 24 or 48 visit window, follows the "virology-first principle" and considers a subject who has a missing plasma HIV-1 RNA, or switches to prohibited ARV regimen or discontinues from the study or study drug for any reason, or dies, as a failure. The percentage of subjects is reported below. The FAS consisted of all subjects who received at least 1 dose of study drug.

End point type Secondary

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: percentage of subjects				
number (not applicable)				
Week 24	25.0	64.5	61.5	48.8
Week 48	50.0	54.8	53.8	39.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with HIV-1 RNA Levels <400 copies/mL at Weeks 24 and 48 using Missing, Discontinuation = Failure (MD=F) Approach

End point title Percentage of Subjects with HIV-1 RNA Levels <400 copies/mL at Weeks 24 and 48 using Missing, Discontinuation = Failure (MD=F) Approach

End point description:

Subjects who have been discontinued from the study, have been lost to follow-up, or have missing HIV-1 RNA data prior to the time point of interest were considered to have HIV-1 RNA levels > lower limit of quantification (LLOQ) . This will be referred to as [non-completer = failure; NC=F] or [missing, discontinuation = failure; MD=F]. The proportion of subjects ($100 \cdot n/N$) is reported below. The FAS consisted of all subjects who received at least 1 dose of study drug.

End point type Secondary

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n=10, 27, 8, 27)	62.5 (38.8 to 86.2)	87.10 (75.3 to 98.9)	69.2 (44.1 to 94.3)	62.8 (48.3 to 77.2)
Week 48 (n=12, 23, 9, 22)	75.0 (53.8 to 96.2)	74.2 (58.8 to 89.6)	69.2 (44.1 to 94.3)	51.2 (36.2 to 66.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with HIV-1 RNA Levels < 48 copies/mL at Weeks 24 and 48 using MD=F Approach

End point title	Percentage of Subjects with HIV-1 RNA Levels < 48 copies/mL at Weeks 24 and 48 using MD=F Approach
-----------------	--

End point description:

Subjects who have been discontinued from the study, have been lost to follow-up, or have missing HIV-1 RNA data prior to the time point of interest were considered to have HIV-1 RNA levels > lower limit of quantification (LLOQ) . This will be referred to as [non-completer = failure; NC=F] or [missing, discontinuation = failure; MD=F]. The proportion of subjects ($100 \cdot n/N$) is reported below. The FAS consisted of all subjects who received at least 1 dose of study drug.

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

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 24 (n=3, 20, 8, 21)	18.8 (0.0 to 37.9)	64.5 (47.7 to 81.4)	61.5 (35.1 to 89.0)	48.8 (33.9 to 63.8)
Week 48 (n=8, 16, 8, 17)	50.0 (25.5 to 74.5)	51.6 (34.0 to 69.2)	61.5 (35.1 to 89.0)	39.5 (24.9 to 54.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with HIV-1 RNA < 400 copies/mL and <48 copies/mL using the time to loss of virologic response algorithm (TLOVR) at Week 48

End point title	Percentage of subjects with HIV-1 RNA < 400 copies/mL and <48 copies/mL using the time to loss of virologic response algorithm (TLOVR) at Week 48
-----------------	---

End point description:

TLOVR is defined as the time from first dose of study medication (Day 1) until the time of virologic failure using the a TLOVR algorithm. The FAS consisted of all subjects who received at least 1 dose of study drug.

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

End point timeframe:

Week 48

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: Percentage of subjects				
number (not applicable)				
<400 copies/mL; TLOVR Responder	62.5	74.2	69.2	48.8
<48 copies/mL; TLOVR Responder	43.8	54.8	46.2	44.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with ≥ 1.0 log₁₀ reduction in HIV-1RNA concentration from baseline to Week 24 and Week 48

End point title	Percentage of Subjects with ≥ 1.0 log ₁₀ reduction in HIV-1RNA concentration from baseline to Week 24 and Week 48
-----------------	---

End point description:

Percentage of subjects with at least a 1.0 log₁₀ reduction in HIV-1 RNA from baseline to Week 24 and Week 48 were tabulated and is presented below. The number of subjects with an observation at specified time points were used to calculate the percentage.

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

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24	92.3 (77.8 to 106.8)	100.0 (100.0 to 100.0)	100.0 (100.0 to 100.0)	93.1 (83.9 to 102.3)
Week 48	100.0 (100.0 to 100.0)	96.2 (88.8 to 103.6)	100.0 (100.0 to 100.0)	88.0 (75.3 to 100.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Change from Baseline in HIV-1 RNA (Original) at Week 24

and Week 48

End point title	Summary of Change from Baseline in HIV-1 RNA (Original) at Week 24 and Week 48
-----------------	--

End point description:

Plasma HIV-1 RNA was determined using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (lower limit of quantification [LLOQ] <48 copies/mL). Blood samples were taken at the time points indicated in the subject evaluation schedule. Screening HIV-1 RNA >1000 copies/ml was used to determine eligibility for the study. The FAS consisted of all subjects who received at least 1 dose of study drug. LOCF was used to impute missing values.

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

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	31	12	39
Units: copies/mL				
arithmetic mean (standard deviation)				
Change from Baseline - Original - Week 24	-271974.6 (± 391843.59)	-38764.0 (± 63688.93)	-58081.0 (± 79720.33)	-57325.7 (± 172108.62)
Change from Baseline - Original - Week 48	-267834.2 (± 378896.88)	-34787.7 (± 60222.60)	-56351.7 (± 76231.03)	-55321.1 (± 173840.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in cluster of differentiation 4 (CD4+) cell count at weeks 24 and 48

End point title	Change from Baseline in cluster of differentiation 4 (CD4+) cell count at weeks 24 and 48
-----------------	---

End point description:

Change from baseline in CD4 cell count to Week 24 and Week 48 were tabulated in aggregated and broken down by age cohort using summary statistics. The FAS consisted of all subjects who received at least 1 dose of study drug. LOCF was used to impute missing values.

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

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	30	12	39
Units: cells/mm ³				
arithmetic mean (standard deviation)				
Week 24	232.7 (± 381.6)	355.8 (± 294.0)	213.9 (± 166.4)	173.6 (± 203.6)

Week 48	275.9 (± 363.4)	362.7 (± 373.5)	167.3 (± 150.9)	168.6 (± 211.0)
---------	-----------------	-----------------	-----------------	-----------------

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD4+ % at weeks 24 and 48

End point title	Change from Baseline in CD4+ % at weeks 24 and 48
-----------------	---

End point description:

Change from baseline in CD4 % to Week 24 and Week 48 were tabulated in aggregated and broken down by age cohort using summary statistics. The FAS consisted of all subjects who received at least 1 dose of study drug. LOCF was used to impute missing values.

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

End point timeframe:

Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	31	12	39
Units: percentage of CD4+ cells				
arithmetic mean (standard deviation)				
Week 24 (n=15, 31, 12, 39)	7.3 (± 5.0)	3.8 (± 7.4)	3.5 (± 4.0)	3.8 (± 6.1)
Week 48 (n=15, 31, 12, 39)	7.5 (± 7.6)	6.0 (± 6.8)	2.5 (± 4.2)	4.6 (± 6.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Protocol Defined Virologic Failure

End point title	Protocol Defined Virologic Failure
-----------------	------------------------------------

End point description:

The occurrence of any one of the following criteria would constitute Virologic failure: A=Decrease from Baseline plasma HIV-1 RNA <1 log₁₀ and plasma HIV-1 RNA >400 copies/mL starting at Week 12 and confirmed at consecutive Week 16; B=Decrease from Baseline plasma HIV-1 RNA <2.0 log₁₀ and plasma HIV-1 RNA >400 copies/mL at Week 24 OR plasma HIV-1 RNA >10,000 copies/mL on and after Week 24, and confirmed within 14 to 21 days; C=Increase from nadir plasma HIV-1 RNA of ≥1 log₁₀ (≥1,000 copies/mL if nadir plasma HIV-1 RNA <48 copies/mL) at any time, and confirmed within 14 to 21 days. The FAS consisted of all subjects who received at least 1 dose of study drug.

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

End point timeframe:

Week 48

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	31	13	43
Units: Number of subjects				
A (measure description above)	0	2	1	5
B (measure description above)	0	0	0	0
C (measure description above)	3	3	2	8
Number of PDVF	3	5	3	13

Statistical analyses

No statistical analyses for this end point

Secondary: Shift Table of Viral Tropism between Screening and Confirmed PDVF Prior to Week 48

End point title	Shift Table of Viral Tropism between Screening and Confirmed PDVF Prior to Week 48
-----------------	--

End point description:

Virus tropism was determined using the Monogram Biosciences Trofile™ viral tropism assay. A shift table of the change in detected tropism from screening to the time of failure was produced in the aggregate and also broken down by age cohort. Subjects who experienced confirmed PDVF through Week 48 with sufficient plasma HIV-1 RNA for virology analysis while receiving MVC. One subject was excluded from summary tables as classified as MSDF response; one subject was analyzed after stopping treatment.

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

End point timeframe:

Screening and Week 48

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	13
Units: Number of subjects				
With valid on-treatment results	2	4	3	11
Tropism at Confirmed PDVF R5	2	3	2	9
Tropism at Confirmed PDVF DM	0	1	1	2
Tropism at Confirmed PDVF X4	0	0	0	0
Tropism at Confirmed PDVF Not Reportable	1	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of the Emergence of reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) resistance associated mutations (RAMs) Between Screening and On-Treatment Confirmed PDVF: Total and by Cohort Prior to Week 48

End point title	Summary of the Emergence of reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) resistance associated mutations (RAMs) Between Screening and On-Treatment Confirmed PDVF: Total and by Cohort Prior to Week 48
-----------------	--

End point description:

Phenotypic and genotypic susceptibility to reverse transcriptase and protease inhibitors was evaluated at screening using the Monogram Biosciences PhenoSense™ GT (PSGT) assay. Samples from a confirmatory PDVF visit or early termination of MVC were planned to be analyzed if the plasma HIV-1 RNA was ≥ 400 copies/mL. Subjects with more than one mutation are counted more than once. One subject was excluded from summary tables as classified as MSDF response; one participant was analyzed after stopping treatment.

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

End point timeframe:

48 weeks

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	13
Units: Number of subjects				
With valid on-treatment results	2	4	3	11
PI Minor (L10L/F, L89L/I/M, V77V/I and K20K/R)	0	0	2	3
PI Major	0	0	0	0
NNRTI (K103K/N and K103N)	0	1	1	1
NRTI M184V	0	0	1	0
Total with emergence	0	1	3	4

Statistical analyses

No statistical analyses for this end point

Secondary: Optimized Background Treatment (OBT) Susceptibility Scores (Net/Overall) by Outcome

End point title	Optimized Background Treatment (OBT) Susceptibility Scores (Net/Overall) by Outcome
-----------------	---

End point description:

Outcome (Response, PDVF or other/remainder) was summarized by the total ARV activity of the background regimen using simple and weighted totals (TOBT and p-wTOBTss, respectively) in the aggregate, categorized as 0, 1, ≥ 2 (TOBT) and 0, 0.5, 1, 1.5 and ≥ 2 (p-wTOBTss) respectively, as well as by screening genotype. Six subjects (Response: n=5; Other failure: n=1) failed to have successful PhenoSense GT analysis at screening, and so a net susceptibility score was not generated. One more subject was not included in the wOBTss analysis due to failed phenotype analysis. However, net susceptibility scores were imputed for simple analysis based on genotype. The FAS consisted of all subjects who received at least 1 dose of study drug. Susceptibility scores indicate the level resistance to the study medication. Scores include: 1 = susceptible and potential low-level resistance; 0.5 = low and intermediate-level resistance; 0 = high-level resistance.

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

End point timeframe:

48 weeks

End point values	Response	PDVF	Other Failure/Remainder	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	23	31	
Units: Percentage of subjects				
number (not applicable)				
Simple score 0	0	0	0	
Simple score 1.0	8.2	4.3	0	
Simple score ≥ 2.0	81.6	95.7	96.8	
Weighted score 0-0.5	6.1	30.4	29.0	
Weighted score 1.0-1.5	53.1	65.2	29.0	
Weighted score ≥ 2.0	28.6	4.3	38.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Change from Baseline in HIV-1 RNA (Log10 copies/mL) at Week 24 and Week 48

End point title	Summary of Change from Baseline in HIV-1 RNA (Log10 copies/mL) at Week 24 and Week 48
End point description:	Plasma HIV-1 RNA was determined using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (lower limit of quantification [LLOQ] <48 copies/mL). Blood samples were taken at the time points indicated in the participant evaluation schedule. Screening HIV-1 RNA >1000 copies/ml was used to determine eligibility for the study.
End point type	Secondary
End point timeframe:	Week 24 and Week 48 post-treatment

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	31	12	39
Units: Log10 Copies/mL				
arithmetic mean (standard deviation)				
Change from Baseline - Log10 - Week 24	-2.4853 (\pm 1.1421)	-2.2324 (\pm 0.8668)	-2.1756 (\pm 1.1854)	-1.6482 (\pm 1.3806)
Change from Baseline - Log10 - Week 48	-2.5831 (\pm 1.2148)	-1.9579 (\pm 1.0861)	-2.0549 (\pm 1.2125)	-1.4591 (\pm 1.4477)

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 5 years

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non-serious in another subject, or 1 subject may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

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

Dictionary version	21.1
--------------------	------

Reporting groups

Reporting group title	Cohort 1
-----------------------	----------

Reporting group description:

>=2 - <6 years of age, MVC liquid formulation

Reporting group title	Cohort 2
-----------------------	----------

Reporting group description:

>=6 - <12 years of age, MVC tablet formulation

Reporting group title	Cohort 3
-----------------------	----------

Reporting group description:

>=6 - <12 years of age, MVC liquid formulation

Reporting group title	Cohort 4
-----------------------	----------

Reporting group description:

>=12 - <18 years of age, MVC tablet formulation

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 16 (31.25%)	5 / 31 (16.13%)	3 / 13 (23.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric fistula			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			

subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Prurigo			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess oral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 43 (23.26%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric fistula			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Prurigo			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteopenia			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tendon disorder			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess oral			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic inflammatory disease			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pulmonary tuberculosis			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)	25 / 31 (80.65%)	10 / 13 (76.92%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			

Tooth extraction subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Pregnancy, puerperium and perinatal conditions Pregnancy subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 2 / 16 (12.50%) 3	1 / 31 (3.23%) 1 1 / 31 (3.23%) 1 1 / 31 (3.23%) 1 1 / 31 (3.23%) 2 1 / 31 (3.23%) 1	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 2 / 13 (15.38%) 2
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all) Breast enlargement subjects affected / exposed occurrences (all) Breast mass	0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0	1 / 31 (3.23%) 2 0 / 31 (0.00%) 0 0	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0

subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Breast pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Bronchospasm			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	3	0	0
Catarrh			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 16 (6.25%)	6 / 31 (19.35%)	2 / 13 (15.38%)
occurrences (all)	2	15	3
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Hyperventilation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Pharyngeal disorder			

subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 16 (0.00%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 31 (6.45%)	1 / 13 (7.69%)
occurrences (all)	0	5	2
Rhonchi			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Allergic cough			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Depression			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Insomnia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nightmare			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Panic disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Aggression			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Flat affect			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood HIV RNA increased	Additional description: From informed consent to 30 days after last MVC dose and within a frequency threshold of 2%.		
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood iron decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hepatic enzyme abnormal			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 2	0 / 13 (0.00%) 0
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	1 / 13 (7.69%) 2
Lipase increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Viral load increased	Additional description: From informed consent to 30 days after last MVC dose and within a frequency threshold of 2%.		
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	1 / 13 (7.69%) 1
Weight increased subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Injury, poisoning and procedural complications			
Accidental exposure to product subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Arthropod sting subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Contusion			

subjects affected / exposed	0 / 16 (0.00%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Foot fracture			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Skin abrasion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Underdose			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Accidental overdose			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Ankle fracture subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Traumatic ulcer subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Traumatic haematoma subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Cardiac disorders Cardiac disorder subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Epilepsy subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Generalised tonic-clonic seizure subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 3	0 / 13 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	2 / 31 (6.45%) 4	2 / 13 (15.38%) 3
Lethargy subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	1 / 13 (7.69%) 1
Somnolence subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Tension headache			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Intellectual disability subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Lymphadenitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	1 / 13 (7.69%) 1
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 3	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Ear and labyrinth disorders			
Deafness subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Ear haemorrhage subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Eye disorders			
Conjunctival pallor subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 2	0 / 13 (0.00%) 0
Conjunctivitis allergic			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 31 (6.45%) 2	0 / 13 (0.00%) 0
Hypermetropia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Refraction disorder subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	2 / 13 (15.38%) 3
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	1 / 13 (7.69%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Anal pruritus subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Dental caries subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	1 / 13 (7.69%) 1
Diarrhoea subjects affected / exposed occurrences (all)	7 / 16 (43.75%) 12	3 / 31 (9.68%) 3	4 / 13 (30.77%) 4
Dyspepsia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0

Flatulence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	3 / 31 (9.68%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Odynophagia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Proctitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Salivary gland mucocoele			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tongue disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	6 / 16 (37.50%)	8 / 31 (25.81%)	3 / 13 (23.08%)
occurrences (all)	15	9	4
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Acne			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Dermatitis			
subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Dermatitis allergic			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Dermatitis contact			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Dermatitis diaper			
subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Dry skin			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	2 / 13 (15.38%) 2
Ecchymosis			
subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Eczema			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	1 / 13 (7.69%) 1
Papule			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Prurigo			
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0

Rash			
subjects affected / exposed	3 / 16 (18.75%)	1 / 31 (3.23%)	1 / 13 (7.69%)
occurrences (all)	4	3	1
Rash pruritic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Urticaria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Urticaria papular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Lipodystrophy acquired			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Neurodermatitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bone swelling			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Joint swelling			

subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Myofascial pain syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Acarodermatitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Angular cheilitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bacterial vaginosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	3 / 16 (18.75%)	3 / 31 (9.68%)	0 / 13 (0.00%)
occurrences (all)	9	12	0

Bullous impetigo			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	2 / 16 (12.50%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	3	2	0
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Fungal skin infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	3 / 16 (18.75%)	0 / 31 (0.00%)	2 / 13 (15.38%)
occurrences (all)	3	0	2
Gastroenteritis viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Herpes virus infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	1 / 16 (6.25%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	1	3	0
Influenza			
subjects affected / exposed	2 / 16 (12.50%)	6 / 31 (19.35%)	3 / 13 (23.08%)
occurrences (all)	4	9	5

Latent tuberculosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lice infestation			
subjects affected / exposed	0 / 16 (0.00%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	4 / 16 (25.00%)	4 / 31 (12.90%)	0 / 13 (0.00%)
occurrences (all)	7	6	0
Oral herpes			
subjects affected / exposed	1 / 16 (6.25%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	1	3	0
Otitis externa			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	6 / 16 (37.50%)	1 / 31 (3.23%)	1 / 13 (7.69%)
occurrences (all)	9	1	1
Otitis media acute			
subjects affected / exposed	2 / 16 (12.50%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	9	2	0
Otitis media chronic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Paronychia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Parotitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Pharyngotonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	3 / 31 (9.68%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Pneumonia bacterial			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	3 / 16 (18.75%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	5	1	0
Sinobronchitis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Tinea capitis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Tinea faciei			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tinea infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 31 (6.45%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Tooth abscess			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tracheitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Tuberculosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	7 / 16 (43.75%)	6 / 31 (19.35%)	2 / 13 (15.38%)
occurrences (all)	23	9	2
Varicella			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 16 (18.75%)	2 / 31 (6.45%)	3 / 13 (23.08%)
occurrences (all)	4	2	4
Vulvovaginitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Mastoiditis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 31 (3.23%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Viral rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 31 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Dehydration subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 2	0 / 13 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0
Insulin resistance subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 31 (3.23%) 1	0 / 13 (0.00%) 0
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 31 (0.00%) 0	0 / 13 (0.00%) 0

Non-serious adverse events	Cohort 4		
Total subjects affected by non-serious adverse events subjects affected / exposed	34 / 43 (79.07%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		

Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Pregnancy, puerperium and perinatal conditions Pregnancy subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0 1 / 43 (2.33%) 1 0 / 43 (0.00%) 0 1 / 43 (2.33%) 1 5 / 43 (11.63%) 7		
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all) Breast enlargement subjects affected / exposed occurrences (all) Breast mass	0 / 43 (0.00%) 0 1 / 43 (2.33%) 1		

subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Breast pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Dysmenorrhoea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Bronchospasm			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Catarrh			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hyperventilation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pharyngeal disorder			

subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Productive cough subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Respiratory disorder subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Rhonchi subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Bronchial hyperreactivity subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Allergic cough subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Psychiatric disorders			
Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Depression subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Hallucination subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Insomnia			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Nightmare			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Panic disorder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Flat affect			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Investigations			
Blood HIV RNA increased	Additional description: From informed consent to 30 days after last MVC dose and within a frequency threshold of 2%.		
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Blood iron decreased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Blood phosphorus decreased			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Cardiac murmur			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hepatic enzyme abnormal			

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Lipase increased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 3		
Viral load increased	Additional description: From informed consent to 30 days after last MVC dose and within a frequency threshold of 2%.		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Weight increased subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Injury, poisoning and procedural complications			
Accidental exposure to product subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Arthropod bite subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Arthropod sting subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Contusion			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Foot fracture			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Injury			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Overdose			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	3		
Thermal burn			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Underdose			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Accidental overdose			

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Ankle fracture subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Traumatic ulcer subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Cardiac disorders Cardiac disorder subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 4		
Epilepsy subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Generalised tonic-clonic seizure subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 10		
Lethargy subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Somnolence subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Tension headache			

<p>subjects affected / exposed occurrences (all)</p> <p>Intellectual disability subjects affected / exposed occurrences (all)</p>	<p>2 / 43 (4.65%) 11</p> <p>0 / 43 (0.00%) 0</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia subjects affected / exposed occurrences (all)</p> <p>Iron deficiency anaemia subjects affected / exposed occurrences (all)</p> <p>Lymphadenitis subjects affected / exposed occurrences (all)</p> <p>Lymphadenopathy subjects affected / exposed occurrences (all)</p> <p>Neutropenia subjects affected / exposed occurrences (all)</p>	<p>3 / 43 (6.98%) 4</p> <p>0 / 43 (0.00%) 0</p> <p>0 / 43 (0.00%) 0</p> <p>5 / 43 (11.63%) 5</p> <p>0 / 43 (0.00%) 0</p>		
<p>Ear and labyrinth disorders</p> <p>Deafness subjects affected / exposed occurrences (all)</p> <p>Cerumen impaction subjects affected / exposed occurrences (all)</p> <p>Ear haemorrhage subjects affected / exposed occurrences (all)</p>	<p>1 / 43 (2.33%) 1</p> <p>1 / 43 (2.33%) 1</p> <p>1 / 43 (2.33%) 1</p>		
<p>Eye disorders</p> <p>Conjunctival pallor subjects affected / exposed occurrences (all)</p> <p>Conjunctivitis allergic</p>	<p>0 / 43 (0.00%) 0</p>		

subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Hypermetropia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Refraction disorder subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 5		
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Anal pruritus subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 3		
Dental caries subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	9 / 43 (20.93%) 10		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 2		

Flatulence			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Gingival swelling			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Odynophagia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Proctitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Salivary gland mucocoele			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Tongue disorder			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	5		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Hyperbilirubinaemia			

subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Acne			
subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Dermatitis			
subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2		
Dermatitis allergic			
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Dermatitis contact			
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Dermatitis diaper			
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Dry skin			
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Ecchymosis			
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Eczema			
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Papule			
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Prurigo			
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		

Rash			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Urticaria papular			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Lipodystrophy acquired			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Neurodermatitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Bone swelling			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Bursitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Joint swelling			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Myofascial pain syndrome			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Abscess			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Acarodermatitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Angular cheilitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Bacterial vaginosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	9		

Bullous impetigo			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Fungal skin infection			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	4		
Gastroenteritis viral			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Herpes virus infection			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		

Latent tuberculosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Lice infestation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Oral herpes			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Otitis externa			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Otitis media acute			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Otitis media chronic			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Paronychia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Parotitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

Pharyngotonsillitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Pneumonia bacterial			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	5		
Sinobronchitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Tinea capitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Tinea faciei			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Tinea infection			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Tracheitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

Tuberculosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Varicella			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Vulvovaginitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Wound infection			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Conjunctivitis bacterial			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Mastoiditis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Viral rash			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Fungal infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pulmonary tuberculosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

Urinary tract infection subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Dehydration subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Insulin resistance subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2009	Amendment 1: Cut-off value for HIV RNA was assay added. Complete abstinence was added as an acceptable form of contraception. Grapefruit-related citrus fruits such as Seville oranges and pomelos were added to the list of concomitant medications to ensure MVC PK was not affected. Instructions for stringent liver function test monitoring were added.
16 August 2010	Amendment 2: ViiV Healthcare was added as the new Sponsor. Sparse PK Sampling was removed at the Early Termination Visits. It was clarified that confirmation virologic failure visit to be conducted 14-21 Days after subject withdrawal. Visit window for Isod visits changed to 1 month. Exclusion criteria for creatinine clearance was mentioned as <90 ml/min. Reference to "Sterilization" and "Post-Menopausal" was deleted. Supply of OBT was clarified. It was clarified that Isoniazid may be allowed on an individual basis and that rifampin was only allowed during Stage 2. It was clarified that an alternate method to Trofile assay could be performed if Trofile assay was not reportable. It was added that an alternate method to PhenoSense GT if result is not reportable. It was clarified that virus susceptibility to MVC would be done at the same time points as the virus susceptibility to OBT.
03 December 2010	Amendment 3: (Country Specific: Kenya and Uganda): It was clarified that local labs may be used for safety testing for sites in Kenya and Uganda. New safety language was added to the AE section.
25 February 2011	Amendment 4: (Country Specific: Brazil): It was clarified that the Sponsor would cover the cost of OBTs if not covered under the Brazil National Program. New safety language was added to the AE section.
01 June 2011	Amendment 5: Information was added to the "Subject Withdrawal" section. Exposure in Utero was renamed Exposure during pregnancy and more instructions were added. Additional details were added to the "Communication of Results by Sponsor" section. The Schedule of Activities section was updated to state that the Screening Period ended on Day 1 and that the follow up period window was increased up to 1 month (this was also done elsewhere it was mentioned in the protocol). It was clarified that in the subjects who had X4 or dual/mixed tropic virus at time of failure, HIV-1 RNA and tropism would be collected at the first ISOD Follow Up visit. It was clarified that the screening BSA will be utilized for initial MVC dose. The objectives of the population PK analyses were clarified.
10 June 2012	Amendment 6: (Country Specific: Brazil): It was clarified that the Sponsor would cover the cost of OBTs if not covered under the Brazil National Program.
09 August 2012	Amendment 7: Appendix 1 was modified (Liver enzyme monitoring to be the same as other ongoing MVC studies). Appendix 5 was added (Rationale for initial MVC dose change for subjects not on potent CYP3A4 inhibitors). Appendix 6 was added (Specific for sites in Brazil). Appendix 7 was added (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events). Changes made were aligned with CT-3: a. Reported medication error as adverse events regardless of whether it is accompanied by an AE. b. AE reporting section was updated.
30 December 2013	Amendment 8: The protocol was amended to extend and ensure the continued supply of the study drug beyond 5 years to subjects benefitting from therapy. It was clarified that the Sponsor would cover the cost of OBTs if it was not covered under the Brazil National Program.

19 May 2014	Amendment 9: In "Schedule of Activities" section and wherever applicable, it was a.) added that at the End of Study visit and follow-up contact, unused medications had to be returned. b.) clarified that study visits in the follow-up period would be up to Week 261. Follow up Visit 9 was added in the Schedule of Activities. The rationale was that the protocol used 52 weeks to equate to a year, however IMPALA drug management system used 48 weeks to equate to a year, resulting in a 5 month gap at the end of 5 years of follow up. c.) clarified that the window in follow-up period was updated to 14days. The rationale was to be consistent with IMPALA drug management system. d.) added that "Contraception Check" would be done at all study visits, per new protocol template. e.) added that creatinine phosphokinase, lipid profile, free T4, TSH and Hepatitis C Virus RNA from Early Termination, were done to be consistent with follow-up period.
-------------	--

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The Disposition section, mentioning "Overall Study" has data only for subject discontinuations up to Week 48, as the study is ongoing. The planned enrollment per protocol was 125 subjects, however, 103 subjects enrolled in the study.

Notes: