



Clinical trial results:

Phase 2 multicentric open-label study of switch from abacavir/lamivudine fixed dose combination plus nevirapine to abacavir/lamivudine/dolutegravir in virologically suppressed HIV-1 infected adults

Summary

EudraCT number	2013-003197-27
Trial protocol	FR
Global end of trial date	10 December 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2022
First version publication date	29 July 2022

Trial information

Trial identification

Sponsor protocol code	RC13_0230
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02067767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Nantes
Sponsor organisation address	5 allée de l'île Gloriette, Nantes, France, 44000
Public contact	Julie LE BARON, CHU de Nantes, 33 0253482835, bp-prom-regl@chu-nantes.fr
Scientific contact	Julie LE BARON, CHU de Nantes, 33 0253482835, bp-prom-regl@chu-nantes.fr

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2015
Global end of trial reached?	Yes
Global end of trial date	10 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to evaluate virologic safety, e.g. maintenance of virologic suppression, after 12 weeks of switch from NVP + ABC/3TC to DTG/ABC/3TC.

Protection of trial subjects:

Therapy should be discontinued for any of the following reasons:

- Subject or Investigator non-compliance
- At the request of the subject, Investigator, or Sponsor
- Confirmed virologic failure: Plasma HIV-1 RNA > 50 c/mL
- Pregnancy (intrauterine)
- Creatinine clearance <50 ml/min
- Liver toxicity
- Grade 4 clinical Adverse Event considered causally related to Investigational Product
- Abacavir hypersensitivity reaction clinically suspected.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	41
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient was recruited the 26/02/2014 and the last patient the 11/12/2014. Patients were recruited at Nantes UH and La Roche sur Yon Hospital.

Pre-assignment

Screening details:

Inclusion criteria :

- Adults \geq 18 years
- HIV-1 infected patient
- On nevirapine (400 mg per day) + ABC/3TC FDC for more than 6 months; Nevirapine 400 mg/day being administered as either 1 x 200 mg IR x 2/day or 2 x 200 mg IR qd or 1 x 400 mg XR qd
- No history of prior virologic failure on antiretroviral therapy

Period 1

Period 1 title	General
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Experimental arm
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Arm description:

Abacavir/Lamivudine/Dolutegravir

Patients switched from their ongoing treatment of ABC/3TC + NVP to ABC/3TC/DTG.

Arm type	Experimental
Investigational medicinal product name	DTG/ABC/3TC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DTG/ABC/3TC tablets are purple, oval, biconvex tablets debossed with "572Tri3" on one side and plain on the other side. The tablet contains 52.62 mg dolutegravir sodium which is equivalent to 50 mg dolutegravir free acid, 702 mg abacavir sulfate which is equivalent to 600 mg abacavir and 300 mg lamivudine. The tablets are packaged into HDPA bottles with child-resistant closures that include induction seals. The bottles contain a dessicant.

Posology: 1 tablet a day during 48 weeks. Patients will have to take the tablet at breakfast until W12, at least.

Route of administration: oral

Number of subjects in period 1	Experimental arm
Started	53
Completed	52
Not completed	1
Adverse event, non-fatal	1

Period 2

Period 2 title	Ancillary study
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Ancillary group
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Arm description:

To further address potential drug-drug interaction, a subgroup of 10 patients (Group 2) had an overlap of 5 days, receiving both NVP-XR and ABC/3TC/DTG, before stopping NVP-XR and continuing solely ABC/3TC/DTG. A 24h pharmacokinetics evaluation of both NVP and DTG was performed in these 10 patients at Day 0 (at steady-state, 5 days after concomitant intake of NVP-XR + ABC/3TC/DTG) and of DTG at Week 2 (14 days after NVP discontinuation).

These patients followed the rest of the study like the other group of patients.

Arm type	Ancillary
Investigational medicinal product name	NVP-XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Posology: one 400 mg tablet of NVP-XR once daily during 5 days.

Route of administration: oral

Investigational medicinal product name	DTG/ABC/3TC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DTG/ABC/3TC tablets are purple, oval, biconvex tablets debossed with "572Tri3" on one side and plain on the other side. The tablet contains 52.62 mg dolutegravir sodium which is equivalent to 50 mg dolutegravir free acid, 702 mg abacavir sulfate which is equivalent to 600 mg abacavir and 300 mg lamivudine. The tablets are packaged into HDPA bottles with child-resistant closures that include induction seals. The bottles contain a dessicant.

Posology: 1 tablet a day during 48 weeks. Patients will have to take the tablet at breakfast until W12, at least.

Route of administration: oral

Number of subjects in period 2^[1]	Ancillary group
Started	10
Day 5 and week 2 PK	10
Completed	10

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only 10 patients did the ancillary study

Baseline characteristics

Reporting groups

Reporting group title	Experimental arm
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Reporting group description:

Abacavir/Lamivudine/Dolutegravir

Patients switched from their ongoing treatment of ABC/3TC + NVP to ABC/3TC/DTG.

Reporting group values	Experimental arm	Total	
Number of subjects	53	53	
Age categorical			
53 HIV-1 infected adults, on stable ABC/3TC + NVP 200 mg bid or 400 mg qd, and HIV-1 RNA < 50 c/mL were included in the study. 41 patients were between 18 and 64 years and 12 patients were older than 65.			
Units: Subjects			
Adults (18-64 years)	41	41	
From 65-84 years	12	12	
Age continuous			
Units: years			
median	52.51		
inter-quartile range (Q1-Q3)	45.75 to 63.36	-	
Gender categorical			
Units: Subjects			
Female	38	38	
Male	15	15	
CDC stage			
Units: Subjects			
Stage A	32	32	
Stage B	12	12	
Stage C	9	9	
Mode of infection			
Units: Subjects			
homosexual/bisexual	26	26	
heterosexual	24	24	
other	3	3	
Age of HIV diagnosis			
Units: years			
median	14.04		
inter-quartile range (Q1-Q3)	10.56 to 18.55	-	
Duration of undetectable viral charge			
Units: years			
median	9.64		
inter-quartile range (Q1-Q3)	6.25 to 12.46	-	
Duration of ABC/3TC + NVP regimen			
Units: year			
median	6.03		
inter-quartile range (Q1-Q3)	4.27 to 6.73	-	

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description: Abacavir/Lamivudine/Dolutegravir Patients switched from their ongoing treatment of ABC/3TC + NVP to ABC/3TC/DTG.	
Reporting group title	Ancillary group
Reporting group description: To further address potential drug-drug interaction, a subgroup of 10 patients (Group 2) had an overlap of 5 days, receiving both NVP-XR and ABC/3TC/DTG, before stopping NVP-XR and continuing solely ABC/3TC/DTG. A 24h pharmacokinetics evaluation of both NVP and DTG was performed in these 10 patients at Day 0 (at steady-state, 5 days after concomitant intake of NVP-XR + ABC/3TC/DTG) and of DTG at Week 2 (14 days after NVP discontinuation). These patients followed the rest of the study like the other group of patients.	

Primary: Percentage of patients with plasma HIV-1 RNA < 50 copies/mL at week 12

End point title	Percentage of patients with plasma HIV-1 RNA < 50 copies/mL at week 12 ^[1]
End point description:	
End point type	Primary
End point timeframe: Week 12	
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: There is no comparison between 2 types of patient	

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percentage				
number (not applicable)				
Percentage of patients with plasma HIV-1 RNA < 50	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with Plasma HIV-1 RNA < 50 copies/ml at W24

End point title	Percentage of patients with Plasma HIV-1 RNA < 50 copies/ml at W24
End point description:	
End point type	Secondary

End point timeframe:

W24

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Percentage	98			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with Plasma HIV-1 RNA < 50 copies/ml at W48

End point title	Percentage of patients with Plasma HIV-1 RNA < 50 copies/ml at W48
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End point description:

End point type	Secondary
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End point timeframe:

W48

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with undetectable plasma viral load (< 1 copies/ml or signal not detected) at W12

End point title	Percentage of patients with undetectable plasma viral load (< 1 copies/ml or signal not detected) at W12
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End point description:

End point type	Secondary
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End point timeframe:

W12

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Percentage	81			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with undetectable plasma viral load (< 1 copies/ml or signal not detected) at W24

End point title	Number of patients with undetectable plasma viral load (< 1 copies/ml or signal not detected) at W24
End point description:	
End point type	Secondary
End point timeframe:	W24

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Number of patients	77			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with undetectable plasma viral load (< 1 copies/ml or signal not detected) at W48

End point title	Number of patients with undetectable plasma viral load (< 1 copies/ml or signal not detected) at W48
End point description:	
End point type	Secondary
End point timeframe:	W48

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Number of patients	67			

Statistical analyses

No statistical analyses for this end point

Secondary: CD4 and CD8 measurements

End point title	CD4 and CD8 measurements
End point description:	
End point type	Secondary
End point timeframe:	
W48	

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: CD/mm3				
median (inter-quartile range (Q1-Q3))				
CD4 at inclusion	737 (557 to 915)			
CD4 at W12	735 (586 to 896)			
CD4 at W24	763 (563.50 to 1017.50)			
CD4 at W48	741.50 (551.50 to 1009)			
CD8 at inclusion	730 (565 to 925)			
CD8 at W12	729 (565 to 934)			
CD8 at W24	806.5 (577 to 980)			
CD8 at W48	812.50 (518.50 to 934.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum creatinine measurements

End point title Serum creatinine measurements

End point description:

End point type Secondary

End point timeframe:

W48

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: µmol/L				
median (inter-quartile range (Q1-Q3))				
creatinine at inclusion	77 (65 to 83)			
creatinine at W12	86 (73 to 98)			
creatinine at W24	86 (76 to 98)			
creatinine at W36	87 (74 to 97)			
creatinine at W48	87 (72 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary albumine/creatinine ratio measurements

End point title Urinary albumine/creatinine ratio measurements

End point description:

End point type Secondary

End point timeframe:

W48

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: mg/mmol				
median (inter-quartile range (Q1-Q3))				
Ratio at inclusion	6.17 (4.55 to 8.33)			

Ratio at W4	5.31 (4.27 to 8)			
Ratio at W24	6.14 (4.25 to 8.43)			
Ratio at W48	5.55 (3.86 to 9.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting lipids measurement

End point title	Fasting lipids measurement
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End point description:

End point type	Secondary
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End point timeframe:

W48

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: g/L				
median (inter-quartile range (Q1-Q3))				
Triglycerides at inclusion	0.98 (0.69 to 1.15)			
Triglycerides at W12	0.89 (0.72 to 1.27)			
Triglycerides W48	0.91 (0.71 to 1.16)			
Cholesterol at inclusion	2.27 (2 to 2.48)			
Cholesterol at W12	1.98 (1.73 to 2.16)			
Cholesterol at W48	1.94 (1.60 to 2.15)			
HDL at inclusion	0.69 (0.56 to 0.84)			
HDL at W12	0.57 (0.47 to 0.71)			
HDL at W48	0.56 (0.46 to 0.69)			
LDL at inclusion	1.32 (1.10 to 1.51)			
LDL at W12	1.10 (0.89 to 1.35)			
LDL at W48	1.17 (0.89 to 1.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Cmax of nevirapine between W0 and W2

End point title	Mean Cmax of nevirapine between W0 and W2
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End point description:

End point type	Secondary
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End point timeframe:

W2

End point values	Ancillary group			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/L				
geometric mean (confidence interval 95%)				
Nevirapine+dolutegravir+abacavir/lamivudine	4408 (3581 to 5426)			
Dolutegravir+ abacavir+ lamivudine	4796 (4077 to 5641)			
ratio	0.92 (0.83 to 1.02)			
nevirapine+dolutegravir+abacavir/lamivudine				

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of patient's satisfaction with HIVTSQs and HIVTSQc questionnaires

End point title	Evaluation of patient's satisfaction with HIVTSQs and HIVTSQc questionnaires
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End point description:

End point type	Secondary
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End point timeframe:

W48

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Patient's satisfaction				
median (inter-quartile range (Q1-Q3))				
HIVTSQS global score at inclusion	54 (51 to 58)			
HIVTSQS general satisfaction at inclusion	28 (26 to 30)			
HIVTSQS lifestyle/ease at inclusion	27 (24 to 29)			
HIVTSQS global score at W48	58 (52.50 to 60)			
HIVTSQS general satisfaction at W48	29 (28 to 30)			
HIVTSQS lifestyle/ease at W48	29 (26.50 to 30)			
HIVTSQC global score at W12	24 (13 to 28)			
HIVTSQC general satisfaction at W12	12 (7 to 14)			
HIVTSQC lifestyle/ease at W12	12 (7 to 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: GFR (MDRD) measurements

End point title	GFR (MDRD) measurements
End point description:	
End point type	Secondary
End point timeframe:	
W48	

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: ml/min				
median (inter-quartile range (Q1-Q3))				
MDRD at inclusion	95.15 (78.70 to 118.66)			
MDRD at W4	79.26 (69.52 to 100.88)			
MDRD at W12	79.94 (67.97 to 95.61)			
MDRD at W24	76.97 (65.19 to 95.24)			

MDRD at W36	77.72 (68.24 to 97.62)			
MDRD at W48	77.92 (66.96 to 92.40)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	overall
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Reporting group description: -

Serious adverse events	overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Coronary artery insufficiency			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 53 (86.79%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			

subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Vascular disorders			
Haematoma	Additional description: 1 patient		
subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed occurrences (all)	8 / 53 (15.09%) 8		
Chest pain			
subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2		
Fatigue			
subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Inflammation			
subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Influenza like illness			
subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3		
Reproductive system and breast disorders			
Epididymal disorder	Additional description: 1 patient		
subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Menometrorrhagia	Additional description: 1 patient		
subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Prostatitis	Additional description: 1 patient		
subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: 1 patient		

subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Epistaxis	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Lung disorder	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Sleep disorder	Additional description: 2 patients		
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Tobacco withdrawal symptoms	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Investigations			
Serum ferritin increased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Creatinine renal clearance decreased			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			

Arthropod sting subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Contusion subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2		
Post traumatic pain subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Tendinitis subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Hand fracture subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Cardiac disorders Pericarditis subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Sciatica subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Cervicobrachial syndrome subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Dizziness subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Eye disorders			

Photopsia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Eyelid irritation			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Anal pruritus			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Anorectal disorder			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	6		
Faeces discoloured			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Faeces soft			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Gingival bleeding			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Haemorrhoids			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Mouth ulceration			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Steatorrhoea			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Tooth disorder			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatocellular injury	Additional description: 2 patients		
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Eczema	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Erythema multiforme	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Night sweats	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Rash erythematous	Additional description: 1 patient		

subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Seborrhoeic dermatitis	Additional description: 1 patient		
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal impairment	Additional description: 3 patients		
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	7		
Intervertebral disc disorder			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Muscle haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Osteoarthritis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Rotator cuff syndrome			

subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Spinal osteoarthritis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		

Otitis media acute			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Parasitic gastroenteritis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Skin infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Viral pharyngitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Viral rhinitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Hypercholesterolaemia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	Criteria for discontinuation of treatment added and investigator's brochure updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26271944>