



## Clinical trial results:

**Phase II trial studying the efficacy of a triplet combination of MLN9708, lenalidomide and dexamethasone as induction prior to, and as consolidation after high-dose therapy with peripheral stem cell transplantation followed by MLN9708 maintenance in the initial management of multiple myeloma in patients younger than 66 years.**

### Summary

EudraCT number	2013-001443-31
Trial protocol	FR
Global end of trial date	17 March 2021

### Results information

Result version number	v1 (current)
This version publication date	19 August 2023
First version publication date	19 August 2023

### Trial information

#### Trial identification

Sponsor protocol code	RC12_0447
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01936532
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	CHU de Nantes
Sponsor organisation address	5 allée de l'île de Gloriette, Nantes, France, 44093
Public contact	Département Promotion, CHU de Nantes, 33 253482835, bp-prom-regl@chu-nantes.fr
Scientific contact	Département Promotion, CHU de Nantes, 33 253482835, 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	17 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2021
Global end of trial reached?	Yes
Global end of trial date	17 March 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary objective:

To evaluate the stringent Complete Response (sCR) rate of the combination of MLN9708, Lenalidomide and Dexamethasone in newly diagnosed multiple myeloma (MM) patients after extended consolidation therapy

Protection of trial subjects:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study.

Strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin) strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, érythromycine and posaconazole) strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), the dietary supplements St John's wort and Ginkgo biloba are prohibited.

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	France: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	38
From 65 to 84 years	4
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

46 patients are included in 10 centers. 42 patients are treated and 4 patients are in screening failure.

### Pre-assignment

Screening details:

Patients diagnosed with multiple myeloma, subjects must have symptomatic myeloma with CRAB criteria and they have measurable disease requiring systemic therapy defined by serum M-component  $\geq 5\text{g/l}$ , urine M-component  $\geq 200\text{ mg/24h}$  or serum FLC  $\geq 100\text{ mg/l}$  are included in this study.

### Pre-assignment period milestones

Number of subjects started	42
Number of subjects completed	42

### Period 1

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

Blinding implementation details:

No blinded

### Arms

Arm title	One arm
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Arm description:

There are one arm

Arm type	Experimental
Investigational medicinal product name	MLN9708
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4.0 mg weekly (Days 1, 8, and 15), followed by 1 week without study drug in a 28-day cycle during induction phase, post-transplant early and late consolidation phases and maintenance therapy.

Number of subjects in period 1	One arm
Started	42
Completed	23
Not completed	19
Physician decision	1
progression	7
Adverse event, non-fatal	6
patient decision	4

Protocol deviation	1
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## Baseline characteristics

### Reporting groups

Reporting group title	essai global
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Reporting group description: -

Reporting group values	essai global	Total	
Number of subjects	42	42	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	38	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous			
Units: years			
median	60		
full range (min-max)	43 to 66	-	
Gender categorical			
Units: Subjects			
Female	21	21	
Male	21	21	

## End points

### End points reporting groups

Reporting group title	One arm
Reporting group description: There are one arm	

### Primary: sCR

End point title	sCR <sup>[1]</sup>
End point description:	

End point type	Primary
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End point timeframe:

To evaluate the sCR rate of the combination of MLN9708, lenalidomide and dexamethasone in newly diagnosed MM patients after extended consolidation therapy at the end of consolidation.

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 are only one arm. We can't enter the data

End point values	One arm			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage				
number (not applicable)	41			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During all study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	All patients
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Reporting group description: -

<b>Serious adverse events</b>	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 42 (47.62%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extradural neoplasm			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell leukaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cementoplasty			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee arthroplasty			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatic operation			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peroneal nerve palsy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Febrile neutropenia</b>			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Thrombocytopenia</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			
<b>Influenza like illness</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
<b>Abdominal pain</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Constipation</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Rectal haemorrhage</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Reproductive system and breast disorders</b>			
<b>Breast calcifications</b>			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Genital prolapse</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Dermatitis exfoliative generalised</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Bone pain</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Influenza</b>			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Periorbital cellulitis</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonia</b>			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonia pneumococcal</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Varicella			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Plasmablastic lymphoma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Jugular vein thrombosis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Orthostatic hypotension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Peripheral venous disease			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	3		

Raynaud's phenomenon subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Surgical and medical procedures Cataract operation subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	17 / 42 (40.48%) 33		
Chest pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Fatigue subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 6		
Feeling jittery subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Inflammation subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5		
Injection site dermatitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Malaise subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Mucosal inflammation subjects affected / exposed occurrences (all)	27 / 42 (64.29%) 29		
Oedema			

<p>subjects affected / exposed occurrences (all)</p> <p>Oedema peripheral subjects affected / exposed occurrences (all)</p> <p>Pyrexia subjects affected / exposed occurrences (all)</p> <p>Vaccination site inflammation subjects affected / exposed occurrences (all)</p>	<p>1 / 42 (2.38%) 1</p> <p>5 / 42 (11.90%) 7</p> <p>22 / 42 (52.38%) 31</p> <p>1 / 42 (2.38%) 1</p>		
<p>Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)</p>	<p>1 / 42 (2.38%) 1</p>		
<p>Respiratory, thoracic and mediastinal disorders Bronchopneumopathy subjects affected / exposed occurrences (all)</p> <p>Cough subjects affected / exposed occurrences (all)</p> <p>Dyspnoea subjects affected / exposed occurrences (all)</p> <p>Dyspnoea exertional subjects affected / exposed occurrences (all)</p> <p>Emphysema subjects affected / exposed occurrences (all)</p> <p>Epistaxis subjects affected / exposed occurrences (all)</p> <p>Lung disorder</p>	<p>1 / 42 (2.38%) 1</p> <p>6 / 42 (14.29%) 6</p> <p>1 / 42 (2.38%) 2</p> <p>1 / 42 (2.38%) 1</p> <p>1 / 42 (2.38%) 1</p> <p>3 / 42 (7.14%) 3</p>		

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nasal polyps			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pharyngeal disorder			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pneumothorax			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	7		
Confusional state			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Depressed mood			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		

Sleep disorder subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Investigations			
Cytomegalovirus test positive subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Intraocular pressure increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Pseudomonas test positive subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Weight increased subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Injury, poisoning and procedural complications			
Eschar subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 2		
Radiation skin injury subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Skin injury subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tooth avulsion subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Congenital, familial and genetic disorders			
Dolichocolon			

subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Cardiac disorders			
Myocardial ischaemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tachycardia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Nervous system disorders			
Carotid arteriosclerosis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Disturbance in attention subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Dysaesthesia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 6		
Dysgeusia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 3		
Dyskinesia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Headache subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 10		
Neuralgia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Neuropathy peripheral			

subjects affected / exposed	12 / 42 (28.57%)		
occurrences (all)	18		
Paraesthesia			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
<b>Blood and lymphatic system disorders</b>			
Anaemia			
subjects affected / exposed	24 / 42 (57.14%)		
occurrences (all)	36		
Bone marrow failure			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Febrile bone marrow aplasia			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	9		
Febrile neutropenia			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Leukopenia			
subjects affected / exposed	11 / 42 (26.19%)		
occurrences (all)	21		
Lymphopenia			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	18		

<p>Macrocytosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 42 (2.38%)</p> <p>1</p>		
<p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>25 / 42 (59.52%)</p> <p>58</p>		
<p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>33 / 42 (78.57%)</p> <p>80</p>		
<p>Ear and labyrinth disorders</p> <p>Tinnitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vertigo positional</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 42 (2.38%)</p> <p>1</p> <p>3 / 42 (7.14%)</p> <p>3</p> <p>1 / 42 (2.38%)</p> <p>1</p>		
<p>Eye disorders</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Keratitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vision blurred</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Visual acuity reduced</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Visual impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 42 (2.38%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p>			

Abdominal pain			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Colitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	14 / 42 (33.33%)		
occurrences (all)	19		
Diarrhoea			
subjects affected / exposed	26 / 42 (61.90%)		
occurrences (all)	44		
Diverticulum			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Enterocolitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Gastric disorder			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Haematochezia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Inguinal hernia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	27 / 42 (64.29%)		
occurrences (all)	45		
Proctalgia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Tooth discolouration			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Umbilical hernia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	14 / 42 (33.33%)		
occurrences (all)	16		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hepatocellular injury			

subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Alopecia</b>			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
<b>Dermatitis contact</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
<b>Dry skin</b>			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
<b>Eczema</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
<b>Erythema</b>			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
<b>Pruritus</b>			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
<b>Rash</b>			
subjects affected / exposed	13 / 42 (30.95%)		
occurrences (all)	28		
<b>Rash maculo-papular</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
<b>Rash papular</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
<b>Rash pruritic</b>			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
<b>Rosacea</b>			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Skin mass			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Toxic skin eruption			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Cystitis haemorrhagic			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypertonic bladder			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal colic			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal cyst			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Urinary hesitation			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	12		
Bone pain			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Bursitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Fracture delayed union			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	12		
Musculoskeletal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Pain in extremity subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Periarthritis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tendon pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tendonitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
<b>Infections and infestations</b>			
Bronchitis subjects affected / exposed occurrences (all)	16 / 42 (38.10%) 17		
Catheter site infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Clostridium colitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Cystitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Ear infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Enterobacter infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Enterococcal infection			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Enterocolitis bacterial			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Epididymitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Fungal skin infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Klebsiella infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Laryngitis			

subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	9		
Oesophageal candidiasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Onychomycosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Oral fungal infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Orchitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Otitis externa			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
parotitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Pseudomonas infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Rhinitis subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4		
Sepsis subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Sinusitis subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 5		
Staphylococcal infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Staphylococcal sepsis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Thrombophlebitis septic subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4		
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 8		
Viral infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4		

Diabetes mellitus			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Vitamin D deficiency			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vitamin K deficiency			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2014	dose modification
06 January 2015	center modification
06 December 2016	investigator brochure modification

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35172566>