Clinical trial results:
A Phase II Trial of combination treatment with Vorinostat, Bortezomib and Dexamethasone in participants with Relapsed Multiple Myeloma

Summary

EudraCT number	2011-005361-20
Trial protocol	GB
Global end of trial date	29 August 2018

Results information

Result version number	v1 (current)
This version publication date	09 November 2019
First version publication date	09 November 2019

Trial information

Trial identification

Sponsor protocol code	HM11/10041

Additional study identifiers

ISRCTN number	ISRCTN08577602
ClinicalTrials.gov id (NCT number)	NCT01720875
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Univeristy of Leeds
Sponsor organisation address	CTRU, Leeds, United Kingdom, LS2 9JT
Public contact	CTRU, University of Leeds CTRU, 0044 0113 343 1478,
Scientific contact	CTRU, University of Leeds CTRU, 0044 0113 343 1478,

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	03 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2015
Global end of trial reached?	Yes
Global end of trial date	29 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the overall response rate (partial response or better) of patients with relapsed multiple myeloma, after combination treatment with vorinostat, bortezomib and dexamethasone.

Protection of trial subjects:

Patients will be monitored closely throughout the trial and attend regular outpatient appointments. Some visits may
involve taking extra blood, urine and bone marrow samples. The additional samples will be taken at the same time as
routine samples so will not involve additional needle punctures. Bone marrow tests are potentially painful but are
undertaken as part of normal care with pain relief and sedation available if required. The potential side effects of the treatments used in this trial are explained within the patient information sheet. Treatment modifications will be made and supportive care given to minimise the side effects.
The frequency of the outpatient appointments during the follow up phase to monitor for disease progression will be
more than standard care. These visits will involve taking a blood and urine sample. routine samples so will not involve additional needle punctures. .

Background therapy:

There are no comparators for this trial all participants received the experimental treatment.

Evidence for comparator:

N/A

Actual start date of recruitment	01 March 2013
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	United Kingdom: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	4
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started September 2013 and was planned to take approximately 12 months. Sixteen patients out of 68 were recruited in 13 months. The trial was halted in October 2014 due to low recruitment due to the availability of other drugs, namely pomalidomide. Vorinostat was also not to be developed further for use in myeloma.

Pre-assignment

Screening details:

Assessments were performed within 21 days prior to registration to ensure they were eligible for the trial. Participants were eligible with 1-3 prior lines of treatment and had to be well enough to receive the treatment in the trial.

Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	16

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Overall trial

Arm description:

All patients received vorinostat, bortezomib and dexamethasone as initial treatment for 8 cycles, patients who have not progressed continue to receive maintenance vorinostat.

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

Dosage and administration details:

400mg days 1-4, 8-11 and 15-18

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m2 days 1, 4, 8, 11

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

Dosage and administration details:

20mg days 1, 2, 4, 5, 8, 9, 11, 12

Number of subjects in period 1	Overall trial
Started	16
Completed	16

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	16	16	
Age categorical			
Mean (SD) 67.6 (8.43) Median (Range) 69.5 (50.0, 78.0)			
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)	4	4	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous			
67.6			
Units: years			
arithmetic mean	67.6		
standard deviation	± 8.34	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	8	8	
ECOG Performance Status			
ECOG Performance Status			
Units: Subjects			
Zero	9	9	
One	7	7	
Treatment Lines			
Number of prior treatment lines at registration			
Units: Subjects			
One	9	9	
Two	5	5	
Three	2	2	
Tumour Stage Diagnosis (ISS criteria)			
Tumour Stage Diagnosis (ISS Criteria) at registration			
Units: Subjects			
One	5	5	
Two	4	4	
Three	3	3	

Missing	4	4	
Paraprotein Type Units: Subjects			
IgG	9	9	
IgA	4	4	
Light chain only	3	3	
Light Chain Type Units: Subjects			
Kappa	9	9	
Lambda	7	7	
Tumour Stage Baseline (ISS criteria) Units: Subjects			
One	11	11	
Two	4	4	
Three	1	1	
Height			
Height at registration			
Units: cm			
arithmetic mean	169.5		
standard deviation	± 10.81	-	
Weight			
Weight at registration			
Units: kilogram(s)			
arithmetic mean	79.5		
standard deviation	± 12.15	-	
BSA			
Body surface area at registration			
Units: square meter			
arithmetic mean	1.9		
standard deviation	± 0.20	-	
Time from original diagnosis to registration Units: months			
arithmetic mean	48.0		
standard deviation	± 32.25	-	
Time from most recent relapse to registration Units: months			
arithmetic mean	1.8		
standard deviation	± 1.78	-	
Time from last dose of systemic anti-myeloma treatment to registration Units: months			
arithmetic mean	14.9		
standard deviation	± 12.91	-	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

All patients received vorinostat, bortezomib and dexamethasone as initial treatment for 8 cycles, patients who have not progressed continue to receive maintenance vorinostat.

Primary: Proportion of participants achieving at least a partial response (PR)

End point title	Proportion of participants achieving at least a partial response (PR)[1]

End point description:

The primary endpoint for the MUKfour trial is overall response rate, measured as the proportion of participants achieving at least a partial response (PR) within 8 cycles of protocol treatment, as defined by modified IWG criteria.
80% confidence intervals correspond to the design of the study, 95% confidence intervals are (54.4, 96.0).

End point type	Primary

End point timeframe:

8 cycles of treatment - 24 weeks

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: statistical analysis is by evlauation of confidence intervals as this is a single arm trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Proportion				
number (confidence interval 80%)	81.3 (62.9 to 92.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants receiving dose reductions of vorinostat or bortezomib, or terminating treatment early due to toxicity

End point title	Proportion of participants receiving dose reductions of vorinostat or bortezomib, or terminating treatment early due to toxicity

End point description:

The dose reduction profile will be summarised as the proportion of participants experiencing a dose reduction of vorinostat or bortezomib (including missed doses due to toxicity) or terminating treatment early due to toxicity during the initial treatment period (i.e. not including maintenance treatment).

End point type	Secondary

End point timeframe:

Duration of the trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Proportion				
number (confidence interval 95%)	75.0 (47.6 to 92.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival at 6 months

End point title	Progression free survival at 6 months

End point description:

Progression free survival is defined as the time from registration until the first documented evidence of disease progression or death. Participants who are alive and progression-free at the time of analysis will be censored on the last day they were known to be alive and progression free. Median PFS was not observed.

End point type	Secondary

End point timeframe:

Duration of the trial treatment

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Proportion				
number (confidence interval 95%)	87.50 (58.60 to 96.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants achieving at least a very good partial response (VGPR)

End point title	Proportion of participants achieving at least a very good partial response (VGPR)

End point description:

Proportion of participants achieving at least a VGPR within 8 cycles includes those participants who achieve a VGPR, CR or sCR. If a participant achieves at least a VGPR within 8 cycles of treatment but subsequently progresses (within 8 cycles) or stops treatment (within 8 cycles), the participant will be classed as achieving at least a VGPR within 8 cycles of treatment

End point type	Secondary

End point timeframe:

within 8 cycles of treatment - 24 weeks

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Proportion				
number (confidence interval 95%)	37.5 (15.2 to 64.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving at least a partial response within 8 cycles

End point title	Number of participants achieving at least a partial response within 8 cycles

End point description:

Maximum response is defined as the proportion of participants achieving each of the response categories sCR, CR, VGPR, PR, MR or SD as their maximum response within 8 cycles of treatment and overall. Participants who do not achieve any of the above as their maximum response will be classed as 'progressive disease'.
Response to treatment is assessed following the Modified IWG Uniform Response Criteria.

End point type	Secondary

End point timeframe:

Duration of treatment and at 8 cycles or 24 weeks.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
Partial response achieved	13			
Not achieved	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum response

End point title	Time to maximum response

End point description:

Time to maximum response is defined as the time from registration until the participant achieves any of the categories sCR, CR, VGPR, PR, MR or SD as their maximum response. Participants who do not achieve maximum response will be censored at the time of disease progression or death, whichever is earlier.
Response to treatment is assessed following the Modified IWG Uniform Response Criteria

End point type	Secondary

End point timeframe:

Duration of treatment

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Months				
median (confidence interval 95%)	1.46 (1.22 to 2.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival at 12 months

End point title	Progression free survival at 12 months

End point description:

Progression free survival is defined as the time from registration until the first documented evidence of disease progression or death. Participants who are alive and progression-free at the time of analysis will be censored on the last day they were known to be alive and progression free. Median PFS was not observed.

End point type	Secondary

End point timeframe:

Duration of the trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Proportion				
number (confidence interval 95%)	54.00 (19.54 to 79.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: number of patients with 1 or more SAEs

End point title	Safety: number of patients with 1 or more SAEs
End point description: Has the participant had an SAE?	
End point type	Secondary
End point timeframe: Duration of the trial.	

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
Yes: SAR No	4 12			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: SAEs

End point title	Safety: SAEs
End point description: Summary statistics of the number of serious adverse events (SAEs) reported	
End point type	Secondary
End point timeframe: Duration of the trial	

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects				
Number of patients with one or more SAEs Number of SAEs reported	4 6			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of SAEs per patient

End point title	Safety: Number of SAEs per patient

End point description:

End point type	Secondary

End point timeframe:

Duration of the trial.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	4[2]			
Units: SAEs				
arithmetic mean (standard deviation)	1.5 (± 0.58)			

Notes:

[2] - 4 patients had an SAE.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Seriousness Criteria for all reported SAEs

End point title	Safety: Seriousness Criteria for all reported SAEs

End point description:

End point type	Secondary

End point timeframe:

Duration of the trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	6[3]			
Units: Seriousness Criteria				
Required/prolonged hospitalisation	6			

Notes:

[3] - There were 6 SAEs in the trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Outcome for all reported SAEs

End point title	Safety: Outcome for all reported SAEs

End point description:

End point type	Secondary

End point timeframe:

Duration of the trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	6[4]			
Units: Outcome				
Recovered	6			

Notes:

[4] - There were 6 SAEs during this trial

Statistical analyses

No statistical analyses for this end point

Secondary: Participants maximum response within 8 cycles

End point title	Participants maximum response within 8 cycles

End point description:

Maximum response is defined as the proportion of participants achieving each of the response categories sCR, CR, VGPR, PR, MR or SD as their maximum response within 8 cycles of treatment and overall. Participants who do not achieve any of the above as their maximum response will be classed as 'progressive disease'.
Response to treatment is assessed following the Modified IWG Uniform Response Criteria.

End point type	Secondary

End point timeframe:

Duration of treatment and at 8 cycles or 24 weeks.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Response				
CR	4			
VGPR	2			
PR	7			
MR	3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival

End point title	Overall survival

End point description:

Overall survival is defined the time from registration to date of death from any cause. Participants alive at the time of analysis will be censored at the last date known to be alive.
At the time of final analysis all participants were alive and no deaths had occurred.

End point type	Other pre-specified

End point timeframe:

Duration of the trial

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Proportion				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From registration until end of duration of the trial.

Adverse event reporting additional description:

Occurrences reflect number of patients with maximum grade experienced not number of AEs experienced.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

Non-serious adverse events are reported by initial treatment (16 patients) and by maintenance treatment (11 patients).

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Hypotension			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Sepsis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders			
Hypertension (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue (initial)			
subjects affected / exposed	15 / 16 (93.75%)		
occurrences (all)	15		
Fatigue (maintenance)			
subjects affected / exposed[1]	7 / 11 (63.64%)		
occurrences (all)	7		
Edema limbs (initial)			

subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Fever (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Pain (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Fever (maintenance)			
subjects affected / exposed[2]	1 / 11 (9.09%)		
occurrences (all)	1		
Pain (maintenance)			
subjects affected / exposed[3]	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dyspnea (initial)			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Epistaxis (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hiccups (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Sore throat (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Psychiatric disorders			
Agitation (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Anxiety (initial)			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Depression (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Insomnia (initial)			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased (initial)			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
Alkaline phosphatase increased (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Creatinine increased (initial)			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Lymphocyte count decreased (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
White blood cell decreased (initial)			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Lymphocyte count decreased (maintenance)			
subjects affected / exposed[4]	1 / 11 (9.09%)		
occurrences (all)	1		
White blood cell decreased (maintenance)			
subjects affected / exposed[5]	2 / 11 (18.18%)		
occurrences (all)	2		
Cardiac disorders			
Palpitations (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Nervous system disorders			
Sensory and Motor Neuropathy (initial)			
subjects affected / exposed	12 / 16 (75.00%)		
occurrences (all)	12		
Sensory Neuropathy (maintenance)			
subjects affected / exposed[6]	7 / 11 (63.64%)		
occurrences (all)	7		
Dizziness (initial)			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
Dysgeusia (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Headache (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Tremor (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia (initial)			
subjects affected / exposed	15 / 16 (93.75%)		
occurrences (all)	15		
Neutropenia (initial)			
subjects affected / exposed	8 / 16 (50.00%)		
occurrences (all)	8		
Thrombocytopenia (initial)			
subjects affected / exposed	13 / 16 (81.25%)		
occurrences (all)	13		
Anaemia (maintenance)			
subjects affected / exposed[7]	8 / 11 (72.73%)		
occurrences (all)	8		
Neutropenia (maintenance)			
subjects affected / exposed[8]	2 / 11 (18.18%)		
occurrences (all)	2		
Thrombocytopenia (maintenance)			

subjects affected / exposed[9]	5 / 11 (45.45%)		
occurrences (all)	5		
Eye disorders			
Blurred vision (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Conjuctivitis (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea (initial)			
subjects affected / exposed	9 / 16 (56.25%)		
occurrences (all)	9		
Nausea (initial)			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	7		
Vomiting (initial)			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Constipation (initial)			
subjects affected / exposed	9 / 16 (56.25%)		
occurrences (all)	9		
Diarrhoea (maintenance)			
subjects affected / exposed[10]	5 / 11 (45.45%)		
occurrences (all)	5		
Nausea (maintenance)			
subjects affected / exposed[11]	3 / 11 (27.27%)		
occurrences (all)	3		
Vomiting (maintenance)			
subjects affected / exposed[12]	2 / 11 (18.18%)		
occurrences (all)	2		
Constipation (maintenance)			
subjects affected / exposed[13]	2 / 11 (18.18%)		
occurrences (all)	2		
Abdominal pain (initial)			

subjects affected / exposed occurrences (all) Bloating (initial) subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Skin and subcutaneous tissue disorders Alopecia (initial) subjects affected / exposed occurrences (all) Rash maculo-papular (initial) subjects affected / exposed occurrences (all) Alopecia (maintenance) subjects affected / exposed[14] occurrences (all) Dry skin (maintenance) subjects affected / exposed[15] occurrences (all)	 3 / 16 (18.75%) 3 2 / 16 (12.50%) 2 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2		
Musculoskeletal and connective tissue disorders Myalgia (initial) subjects affected / exposed occurrences (all) Back pain (maintenance) subjects affected / exposed[16] occurrences (all) Myalgia (maintenance) subjects affected / exposed[17] occurrences (all)	 4 / 16 (25.00%) 4 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Infections and infestations Sepsis (initial) subjects affected / exposed occurrences (all) Upper respiratory infection (initial) subjects affected / exposed occurrences (all) Urinary tract infection (initial)	 1 / 16 (6.25%) 1 2 / 16 (12.50%) 2		

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eye infection (maintenance)			
subjects affected / exposed[18]	1 / 11 (9.09%)		
occurrences (all)	1		
Skin infection (maintenance)			
subjects affected / exposed[19]	1 / 11 (9.09%)		
occurrences (all)	1		
Upper respiratory infection (maintenance)			
subjects affected / exposed[20]	2 / 11 (18.18%)		
occurrences (all)	2		
Urinary tract infection (maintenance)			
subjects affected / exposed[21]	1 / 11 (9.09%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Dehydration (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hyperglycemia (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hypoalbuminemia (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hypocalcemia (initial)			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hypokalemia (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hyponatraemia (initial)			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hypophosphatemia (initial)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects

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Justification: These are reported for patients receiving maintenance treatment (n=11)

[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[19] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[20] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

[21] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: These are reported for patients receiving maintenance treatment (n=11)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported