Clinical trial results:
A phase 1/2a, dose escalation study of CHR-3996 in combination with tosedostat in subjects with relapsed, refractory multiple myeloma

Summary

EudraCT number	2011-001914-33
Trial protocol	GB
Global end of trial date	30 October 2017

Results information

Result version number	v1 (current)
This version publication date	08 November 2018
First version publication date	08 November 2018

Trial information

Trial identification

Sponsor protocol code	HM11/9825

Additional study identifiers

ISRCTN number	ISRCTN24989786
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	CTRU, Leeds, United Kingdom, LS2 9JT
Public contact	Louise Flanagan, CTRU, University of Leeds , 44 1133431477, medctco@leeds.ac.uk
Scientific contact	Sarah Brown, CTRU, University of Leeds , 44 1133431477, medctco@leeds.ac.uk

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	11 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2016
Global end of trial reached?	Yes
Global end of trial date	30 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

During the dose escalation phase, the purpose of the study is to determine the maximum tolerated dose (MTD) of CHR-3996 and tosedostat administered in combination in subjects with relapsed or refractory multiple myeloma.

In the dose expansion phase the purpose of the study is to determine the safety profile of CHR-3996 and tosedostat administered in combination and to estimate the response rate.

Protection of trial subjects:

N/A

Background therapy:

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

Evidence for comparator:

N/A

Actual start date of recruitment	01 August 2011
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: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	14
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from NHS Hospitals in the UK with ethical and regulatory approval. Participants were approached during their usual clinic visits by a doctor and consented if they were willing to take part. They were registered to the trial and eligibility checked. The recruitment period was July 2012 - December 2015.

Pre-assignment

Screening details:

Participants were screened for eligibility once consented and registered to the trial to ensure they met all criteria.

Period 1

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

Arms

Arm title	Safety analysis population

Arm description:

The safety analysis population includes all participants who received at least one dose of trial treatment. Only participants, for whom written informed consent has not been received, are not included in this population.

Arm type	Experimental
Investigational medicinal product name	CHR-3996
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

20mg/20mg/40mg/40mg once daily for 28 day cycle

Investigational medicinal product name	tosedostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

60mg/0mg/0mg/60mg once daily for 28 day cycle

Number of subjects in period 1[1]	Safety analysis population
Started	22
Completed	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There were 27 patients recruited to the trial, but only 22 went on to receive treatment. This is why the number of patients in the safety analysis population (baseline period) does not match the number enrolled in the trial. This was agreed with the Scientific Lead.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	22	22	
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)	11	11	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous			
Age at registration			
Units: years			
arithmetic mean	62.9		
standard deviation	± 8.7	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	12	12	
Missing	1	1	
ECOG status Units: Subjects			
Zero	4	4	
One	18	18	
Previous treatment lines Units: Subjects			
Two	1	1	
Three	3	3	
Four	7	7	
Five	4	4	
Six	1	1	
Seven	2	2	
Eight	2	2	
Nine	1	1	
Missing	1	1	
Tumour Stage Units: Subjects			
One	5	5	

Two	11	11	
Three	5	5	
Missing	1	1	
Paraprotein type Units: Subjects			
IgG	15	15	
IgA	4	4	
Light chain only	3	3	
Light chain type Units: Subjects			
Kappa	13	13	
Lambda	9	9	
Systolic BP Units: mmHg			
arithmetic mean	127.0		
standard deviation	± 17.21	-	
Diastolic BP Units: mmHg			
arithmetic mean	76.8		
standard deviation	± 7.58	-	
Pulse rate Units: bpm			
arithmetic mean	80.8		
standard deviation	± 11.22	-	
Temperature Units: degrees celcius			
arithmetic mean	36.5		
standard deviation	± 0.37	-	
QTcF interval Units: msec			
arithmetic mean	393.1		
standard deviation	± 82.03	-	
Time from most recent relapse to registration			
Time from most recent relapse to registration date			
Units: Months			
arithmetic mean	1.3		
standard deviation	± 1.2	-	
Time from last dose of systemic anti-myeloma treatment to registration Units: Months			
arithmetic mean	1.5		
standard deviation	± 1.81	-	

Subject analysis sets

Subject analysis set title	Primary analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined by all participants registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.

Subject analysis set title	Non-recommended dose analysis set

Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined by all participants who were not registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.

Reporting group values	Primary analysis set	Non-recommended dose analysis set	
Number of subjects	10	12	
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)	6	5	
From 65-84 years	4	7	
85 years and over	0	0	
Age continuous			
Age at registration			
Units: years			
arithmetic mean	61.2	64.2	
standard deviation	± 9.34	± 8.38	
Gender categorical Units: Subjects			
Female	4	5	
Male	5	7	
Missing	1	0	
ECOG status Units: Subjects			
Zero	2	2	
One	8	10	
Previous treatment lines Units: Subjects			
Two	1	0	
Three	0	3	
Four	6	1	
Five	0	4	
Six	0	1	
Seven	1	1	
Eight	0	2	
Nine	1	0	
Missing	1	0	
Tumour Stage Units: Subjects			
One	2	3	
Two	5	6	
Three	3	2	
Missing	0	1	
Paraprotein type			

Units: Subjects			
IgG	7	8	
IgA	2	2	
Light chain only	1	2	
Light chain type Units: Subjects			
Kappa	6	7	
Lambda	4	5	
Systolic BP Units: mmHg			
arithmetic mean	117.5	134.8	
standard deviation	± 13.71	± 16.21	
Diastolic BP Units: mmHg			
arithmetic mean	75.4	77.9	
standard deviation	± 9.18	± 6.13	
Pulse rate Units: bpm			
arithmetic mean	84.6	77.6	
standard deviation	± 9.50	± 11.91	
Temperature Units: degrees celcius			
arithmetic mean	36.6	36.5	
standard deviation	± 0.20	± 0.47	
QTcF interval Units: msec			
arithmetic mean	409.4	379.6	
standard deviation	± 18.15	± 110.16	
Time from most recent relapse to registration			
Time from most recent relapse to registration date			
Units: Months			
arithmetic mean	0.7	1.7	
standard deviation	± 0.46	± 1.38	
Time from last dose of systemic anti-myeloma treatment to registration Units: Months			
arithmetic mean	0.5	2.3	
standard deviation	± 0.24	± 2.17	

End points

End points reporting groups

Reporting group title	Safety analysis population

Reporting group description:

The safety analysis population includes all participants who received at least one dose of trial treatment. Only participants, for whom written informed consent has not been received, are not included in this population.

Subject analysis set title	Primary analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined by all participants registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.

Subject analysis set title	Non-recommended dose analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined by all participants who were not registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.

Primary: Dose escalation phase: Dose limiting toxicity (DLT)

End point title	Dose escalation phase: Dose limiting toxicity (DLT)[1]

End point description:

The number of participants recruited to the dose escalation phase of the study, experiencing DLTs within the first 28-day cycle of CHR-3996 and tosedostat.

DLT was defined by any of the following events:
- Any non haematological toxicity ≥ Grade 3 according to NCI CTCAE Version 4 which fails to return to ≤Grade 1 or baseline after 7 days. Nausea, vomiting, diarrhoea and electrolyte imbalances will be considered DLTs only if they reach ≥ Grade 3 severity despite adequate supportive care measures.
- Grade 4 neutropenia with sepsis or Grade 4 neutropenia lasting >7 days despite adequate supportive care measures.
- Any grade 4 thrombocytopenia which fails to return to baseline after 7 days with platelet support
- Omission of > 7 days for resumption of treatment due to toxicity (i.e an inability to commence cycle 2 until after day 8)
- Treatment related death

End point type	Primary

End point timeframe:

DLTs were assessed during the first cycle of treatment, up to the administration of cycle 2 day 1 of dose escalation patients.

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: As this is a phase I study, the primary endpoint related to data summaries only.

End point values	Safety analysis population			
Subject group type	Reporting group			
Number of subjects analysed	15[2]			
Units: Number of DLTs				
20mg CHR-3996, 0mg Tosedostat - DLT	0			
20mg CHR-3996, 0mg Tosedostat - no DLT	3			
40mg CHR-3996, 0mg Tosedostat - DLT	0			
40mg CHR-3996, 0mg Tosedostat - no DLT	3			
40mg CHR-3996, 60mg Tosedostat - DLT	1			

40mg CHR-3996, 60mg Tosedostat - no DLT	2			
20mg CHR-3996, 60mg Tosedostat - DLT	0			
20mg CHR-3996, 60mg Tosedostat - no DLT	6			

Notes:

[2] - 15 participants were recruited to the dose escalation phase and were evaluable for DLTs

Statistical analyses

No statistical analyses for this end point

Primary: Expansion phase: Stable disease

End point title	Expansion phase: Stable disease[3]

End point description:

The proportion of participants achieving at least stable disease (SD) after 4 cycles of CHR-3996 and tosedostat.

Response to treatment is assessed after a participant has received 4 cycles of treatment. If a participant stops treatment within 4 months of registration for reasons other than disease progression, response will be assessed every 4 weeks until 4 months post-registration or disease progression, whichever is earlier. If a participant progresses within 4 cycles of treatment, the participant will be classed as not achieving at least stable disease after 4 cycles of treatment.

End point type	Primary

End point timeframe:

after 4 cycles of CHR-3996 and tosedostat

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is a phase I study, the primary endpoint related to data summaries only.

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Proportion				
number (confidence interval 95%)	30 (6.7 to 65.2)	16.7 (2.1 to 48.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum response (6 cycles)

End point title	Maximum response (6 cycles)

End point description:

The proportion of participants with each maximum response category within 6 cycles of therapy.

Maximum response is defined as the maximum response category achieved within the corresponding assessment period, for each participant. The response categories are: stringent complete response (sCR); complete response (CR); very good partial response (VGPR); partial response (PR); minimal

response (MR); stable disease (SD)/no change (NC).

End point type	Secondary
End point timeframe: within 6 cycles	

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subjects				
PR	1	0		
SD or NC	4	9		
PD	4	3		
Participant died within first cycle of treatment	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum response (overall)

End point title	Maximum response (overall)

End point description:

The proportion of participants with each maximum response category to therapy overall.

Maximum response is defined as the maximum response category achieved within the corresponding assessment period, for each participant. The response categories are: stringent complete response (sCR); complete response (CR); very good partial response (VGPR); partial response (PR); minimal response (MR); stable disease (SD)/no change (NC).

End point type	Secondary
End point timeframe: over the whole trial	

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subjects				
PR	1	0		
MR	1	0		
SD or NC	3	9		

PD	4	3		
Participant died within first cycle of treatment	1	0		

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 was defined as the time from registration until the patient achieved their maximum response. Those who did not achieve maximum response, are censored at the date of disease progression.

End point type	Secondary

End point timeframe:

registration until patient achieved their maximum response

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[4]	9[5]		
Units: Months				
median (confidence interval 95%)	1.84 (1.09 to 8.65)	1.45 (1.22 to 1.81)		

Notes:

[4] - Of the 10 participants in the primary analysis set, only 5 achieved a maximum response.

[5] - Of the 12 participants in the non-RD analysis set, only 9 achieved a maximum response.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression free survival is defined as the time from registration to first documented evidence of disease progression or death. Participants who, at the time of analysis, have not progressed will be censored at the last date they were known to be alive and progression free.

Calculated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

registration until first documented evidence of disease progression or death.

End point values	Primary analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Month				
median (confidence interval 95%)	1.8 (0.92 to 4.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: CHR-3996 dose reduction (toxicity)

End point title	CHR-3996 dose reduction (toxicity)

End point description:

Number of dose reductions, is defined as the number of participants experiencing at least 1 CHR-3996 dose reduction due to toxicity.

End point type	Secondary

End point timeframe:

whilst receiving trial treatment

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subjects				
No reduction	8	10		
Reduction	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Tosedostat dose reduction (toxicity)

End point title	Tosedostat dose reduction (toxicity)

End point description:

Number of dose reductions, is defined as the number of participants experiencing at least 1 tosedostat dose reduction due to toxicity.

End point type	Secondary

End point timeframe:

whilst receiving trial treatment

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subject				
No reduction	9	12		
Reduction	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance

End point title	Treatment compliance

End point description:

Participants will be regarded as compliant to treatment where treatment is received as per protocol until withdrawal from trial treatment, without missing >5 days of either CHR-3996 or tosedostat in the first cycle for reasons other than toxicity, or >5 days of either treatment in any subsequent cycle.

End point type	Secondary

End point timeframe:

until withdrawal from trial treatment

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subjects				
Missed more than 5 days dosing	6	8		
Did not miss more than 5 days dosing	4	4		

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:

The number of patients with one or more serious adverse reaction (SAR)/serious adverse event (SAE).

End point type	Secondary

End point timeframe:

time of written informed consent until 30 days post cessation of trial therapy.

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subjects				
Yes: SAR	2	3		
Yes: SAE	7	4		
No	1	5		

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:

time of written informed consent until 30 days post cessation of trial therapy.

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Subjects/SAEs				
Number of patients with one of more SAE	9	7		
Number of SAEs reported	14	8		

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:

Summary statistics of the number of serious adverse events (SAEs) per patient.

End point type	Secondary

End point timeframe:

time of written informed consent until 30 days post cessation of trial therapy.

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[6]	7[7]		
Units: SAEs				
arithmetic mean (standard deviation)				
Number of SAEs per patient	1.6 (± 0.88)	1.1 (± 0.38)		

Notes:

[6] - 9 out of the 10 participants in the primary population experienced an SAE

[7] - 7 out of the 12 participants in the non-RD population experienced an SAE

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival is defined as the time from registration to date of death from any cause. Participants who were still alive at the time of analysis were censored at the last date they were known to be alive.

End point type	Secondary

End point timeframe:

registration until date of death or final analysis, which was sooner.

End point values	Primary analysis set	Non-recommended dose analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	12		
Units: Deaths				
Died	5	2		
Not died	5	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring for all participants from the time of written informed consent until 30 days post cessation of trial therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety population includes all participants who have received at least one dose of any trial treatment. Only patients for whom written informed consent was not received are excluded.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 22 (72.73%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	1 / 7		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		
Epistaxis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 7		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 7		
Gastrointestinal disorders			
Diarrhoea, vomiting and C-difficile			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		
Dehydration, vomiting and nausea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		
Nausea and diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		
Respiratory, thoracic and mediastinal disorders			
Chest infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 7		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		
Raised creatinine			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 7		

Acute kidney injury / creatinine increased				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 7			
Infections and infestations				
Upper respiratory tract infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 7			
Soft tissue infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 7			
Urinary tract infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 7			
Lung infection				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 7			
Infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 7			
Fever				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 7			
Flu like symptoms				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 7			

Fever and upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 7		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 22 (77.27%)		
occurrences (all)	17		
Fever			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Edema limbs			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Lethargy			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Localized edema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Other			
subjects affected / exposed	12 / 22 (54.55%)		
occurrences (all)	12		
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dyspnea			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Hiccups			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Insomnia			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Confusion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Investigations			
Platelet count decreased			
subjects affected / exposed	15 / 22 (68.18%)		
occurrences (all)	15		
White blood cell count decreased			
subjects affected / exposed	12 / 22 (54.55%)		
occurrences (all)	12		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Creatinine increased			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	6		
CPK increased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Investigations - other, specify			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		

Weight loss			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
INR increased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Alkaline phosphatase increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cardiac disorders - other, specify			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Ventricular arrhythmia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	8		
Dysgeusia			

subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nervous system disorders - other, specify			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
radiculitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 22 (72.73%)		
occurrences (all)	16		
Hematoma			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Oral haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cataracts			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Watering eyes			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 22 (59.09%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	15 / 22 (68.18%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Enterocolitis infectious			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	7		
Mucositis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

Gastrointestinal disorders - other, specify			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Flushing			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin ulceration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
allergic rhinitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hyperuricemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
neck pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	8		
Lung infection			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Infections and infestations - other, specify			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Soft tissue infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Flu like symptoms			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Tooth infection			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	6		
Hypercalcemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Anorexia			
subjects affected / exposed	14 / 22 (63.64%)		
occurrences (all)	14		
Dehydration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hypermagnesemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypernatremia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypocalcemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
hyperglycemia			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2011	Protocol v3.0
14 March 2012	Protocol v4.0
16 August 2013	Protocol v5
04 July 2014	Protocol v6
11 September 2014	Protocol v7

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported