Clinical trial results:
A Phase 1b/2 Multi-Center, Open Label, Dose-Escalation Study To Determine The Maximum Tolerated Dose, Safety, And Efficacy Of Acy-1215 (Ricolinostat) In Combination With Pomalidomide And Low-Dose Dexamethasone In Patients With Relapsed-And Refractory Multiple Myeloma

Summary

EudraCT number	2014-002338-29
Trial protocol	IT GR
Global end of trial date	29 February 2024

Results information

Result version number	v1 (current)
This version publication date	27 February 2025
First version publication date	27 February 2025

Trial information

Trial identification

Sponsor protocol code	ACE-MM-102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

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	19 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2024
Global end of trial reached?	Yes
Global end of trial date	29 February 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1b:
To determine the maximum tolerated dose (MTD), or if not present, the recommended Phase 2 dose and schedule of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.
Phase 2:
To determine the efficacy of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone as treatment for patients with relapsed-and-refractory MM as assessed by overall response rate.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 62
Worldwide total number of subjects	103
EEA total number of subjects	25

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	52
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of Phase 1b (dose finding segment) part and Phase 2(dose expansion segment) part.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b - ACY-1215 Dose Level 1

Arm description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	ACY-1215
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

160 mg/day on Days 1-21 of a 28-day cycle

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

Dosage and administration details:

40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 mg/day on Days 1-21 of a 28-day cycle

Arm title	Phase 1b - ACY-1215 Dose Level 3

Arm description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Arm type	Experimental

Investigational medicinal product name	ACY-1215
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

160 mg twice/day on Days 1-21 of a 28-day cycle

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

Dosage and administration details:

40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 mg/day on Days 1-21 of a 28-day cycle

Arm title	Phase 2 - ACY-1215 Dose Level 1

Arm description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	ACY-1215
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

160 mg/day on Days 1-21 of a 28-day cycle

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

Dosage and administration details:

40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 mg/day on Days 1-21 of a 28-day cycle

Arm title	Phase 2 - ACY-1215 Dose Level 3

Arm description:	
Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Arm type	Experimental
Investigational medicinal product name	ACY-1215
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use
Dosage and administration details:	
160 mg twice/day on Days 1-21 of a 28-day cycle	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle.	
Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
4 mg/day on Days 1-21 of a 28-day cycle	

Number of subjects in period 1	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1
Started	3	4	85
Efficacy evaluable population	3	4	77
Safety population	3	4	85
Completed	0	0	0
Not completed	3	4	85
Physician decision	-	-	3
Adverse event, non-fatal	-	-	15
Withdrawal by participant	-	-	8
Other reasons	-	-	1
Progressive disease	3	4	57
Lost to follow-up	-	-	1

Number of subjects in period 1	Phase 2 - ACY-1215 Dose Level 3
Started	11
Efficacy evaluable population	7
Safety population	11

Completed	0
Not completed	11
Physician decision	-
Adverse event, non-fatal	2
Withdrawal by participant	1
Other reasons	-
Progressive disease	8
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b - ACY-1215 Dose Level 1
Reporting group description:	
Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Reporting group title	Phase 1b - ACY-1215 Dose Level 3
Reporting group description:	
Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Reporting group title	Phase 2 - ACY-1215 Dose Level 1
Reporting group description:	
Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Reporting group title	Phase 2 - ACY-1215 Dose Level 3
Reporting group description:	
Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	

Reporting group values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1
Number of subjects	3	4	85
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	2	2	42
>=65 years	1	2	43
Age continuous Units: years			
arithmetic mean	62.0	68.0	64.6
standard deviation	± 14.42	± 6.48	± 8.83
Sex: Female, Male Units: Participants			
Female	2	1	40
Male	1	3	45
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	7
White	3	4	72
More than one race	0	0	0
Unknown or Not Reported	0	0	2
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	0	0	1
Not Hispanic or Latino	3	4	81
Unknown or Not Reported	0	0	3

Reporting group values	Phase 2 - ACY-1215 Dose Level 3	Total	
Number of subjects	11	103	
Age Categorical Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	4	50	
>=65 years	7	53	
Age continuous Units: years			
arithmetic mean	67.1		
standard deviation	± 8.81	-	
Sex: Female, Male Units: Participants			
Female	4	47	
Male	7	56	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	0	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	8	
White	10	89	
More than one race	0	0	
Unknown or Not Reported	0	2	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	11	99	
Unknown or Not Reported	0	3	

End points

End points reporting groups

Reporting group title	Phase 1b - ACY-1215 Dose Level 1
Reporting group description:	
Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Reporting group title	Phase 1b - ACY-1215 Dose Level 3
Reporting group description:	
Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Reporting group title	Phase 2 - ACY-1215 Dose Level 1
Reporting group description:	
Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Reporting group title	Phase 2 - ACY-1215 Dose Level 3
Reporting group description:	
Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	
Subject analysis set title	Phase 1b - ACY-1215
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received either 160 mg ACY-1215 once per day (Dose Level 1) or 160 mg ACY-1215 twice per day (Dose Level 3) and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.	

Primary: Maximum Tolerated Dose (MTD) of ACY-1215- Phase 1b

End point title	Maximum Tolerated Dose (MTD) of ACY-1215- Phase 1b[1]
End point description:	
The maximum tolerated dose (MTD) was defined as the highest dose level at which no more than 1 of 6 patients experienced a dose-limiting toxicity (DLT) within the first 28-day cycle. If no more than 1 of these 6 patients experienced a DLT within the first 28-day cycle, then the last dose level enrolled to meet these criteria was identified as the recommended dose for the Phase 2 segment of the study.	
End point type	Primary
End point timeframe:	
From first dose until the end of Phase 1b (up to a maximum of approximately 50 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: Only descriptive statistics were planned for this endpoint.

End point values	Phase 1b - ACY-1215			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: mg/day	320			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) per Investigator - Phase 2

End point title	Overall Response Rate (ORR) per Investigator - Phase 2[2][3]

End point description:

Overall response rate (ORR) is defined as the percentage of participants with a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).
sCR:
- No detectable myeloma cells in the bone marrow.
- Normal free light chain ratio.
- Absence of clonal cells in the bone marrow.

CR:
- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- Less than 5% plasma cells in the bone marrow.

VGPR:
- Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or
- At least a 90% reduction in serum M-protein plus urine M-protein level less than 100 mg per 24 hours.

PR:
- At least a 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by at least 90% or to less than 200 mg per 24 hours.
- For patients with non-secretory myeloma, a reduction of at least 50% in the size of soft tissue plasmacytomas is required.

End point type	Primary

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Prespecified to be reported for Phase 2 only.

End point values	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	7		
Units: Percent of Participants				
number (confidence interval 95%)	39.0 (28.0 to 50.8)	71.4 (29.0 to 96.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

Time to response (TTR) was defined as the time from first dose of study treatment to the first documentation of response (either partial response (PR) or complete response (CR)).

CR:
- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- Less than 5% plasma cells in the bone marrow.

PR:
- At least a 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by at least 90% or to less than 200 mg per 24 hours.
- For patients with non-secretory myeloma, a reduction of at least 50% in the size of soft tissue plasmacytomas is required.

End point type	Secondary

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[4]	30	5
Units: Weeks				
arithmetic mean (full range (min-max))	8.50 (4.1 to 12.9)	(to)	10.83 (4.1 to 40.1)	12.96 (7.9 to 31.9)

Notes:

[4] - No responders in Ph1b at DL3

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

Duration of Response (DOR) was defined as the time from first partial response (PR) or complete response (CR) to the first documentation of progressive disease (PD) or death.

PR:
- >= 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by >= 90% or to less than 200 mg per 24 hours.
- For non-secretory myeloma, a reduction of >= 50% in size of soft tissue plasmacytomas.

CR:
- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- < 5% plasma cells in the bone marrow.

PD:
- Increase of 25% or more from nadir in serum M-protein, absolute increase of >= 0.5 g/dL.
- Increase of 25% or more from nadir in 24-hour urinary M-protein, absolute increase of >=200 mg/24 hours.
- Increase of 25% or more in the percentage of bone marrow plasma cells, absolute increase of >=10%.

Calculated using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[5]	30	5
Units: Weeks				
median (confidence interval 95%)	20.10 (4.10 to 36.10)	(to)	30.30 (13.10 to 43.10)	62.75 (54.75 to 121.6)

Notes:

[5] - No responders in Ph1b at DL3

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to progression (TTP) was defined as the time from the date of first dose to the date of first documentation of progressive disease (PD).
PD:

- Increase of 25% or more from nadir in serum M-protein, absolute increase of >= 0.5 g/dL.
- Increase of 25% or more from nadir in 24-hour urinary M-protein, absolute increase of >=200 mg/24 hours.
- Increase of 25% or more in the percentage of bone marrow plasma cells, absolute increase of >=10%.
- New bone lesions or soft tissue plasmacytomas or increase size of existing bone lesions or soft tissue plasmacytomas.
- Hypercalcemia attributed to myeloma.

End point type	Secondary

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	77	7
Units: Weeks				
arithmetic mean (full range (min-max))	22.43 (8.1 to 48.9)	6.20 (4.1 to 8.1)	29.82 (3.9 to 169.1)	83.22 (7.7 to 183.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per Central Adjudication Committee

End point title	Overall Response Rate (ORR) per Central Adjudication Committee

End point description:

Overall response rate (ORR) is defined as the percentage of participants with a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).
sCR:
- No detectable myeloma cells in the bone marrow.
- Normal free light chain ratio.
- Absence of clonal cells in the bone marrow.

CR:
- Negative immunofixation on the serum and urine.
- Disappearance of any soft tissue plasmacytomas.
- Less than 5% plasma cells in the bone marrow.

VGPR:
- Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or
- At least a 90% reduction in serum M-protein plus urine M-protein level less than 100 mg per 24 hours.

PR:
- At least a 50% reduction in serum M-protein.
- Reduction in 24-hour urinary M-protein by at least 90% or to less than 200 mg per 24 hours.
- For patients with non-secretory myeloma, a reduction of at least 50% in the size of soft tissue plasmacytomas is required

End point type	Secondary

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	0[8]	0[9]
Units: Percent of Participants				
number (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[6] - Data not collected

[7] - Data not collected

[8] - Data not collected

[9] - Data not collected

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Progression-free survival (PFS) was defined as the time from first dose of study treatment to the first documentation of progressive disease (PD) or death from any cause during study
PD:
- Increase of 25% or more from nadir in serum M-protein, absolute increase of >= 0.5 g/dL.
- Increase of 25% or more from nadir in 24-hour urinary M-protein, absolute increase of >=200 mg/24 hours.
- Increase of 25% or more in the percentage of bone marrow plasma cells, absolute increase of >=10%.
- New bone lesions or soft tissue plasmacytomas or increase size of existing bone lesions or soft tissue plasmacytomas.
- Hypercalcemia attributed to myeloma.

Calculated using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

From first dose until disease progression, study drug toxicity, end of study, or death due to any cause (up to approximately 120 months).

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	77	7
Units: Weeks				
median (confidence interval 95%)	22.43 (8.10 to 48.90)	6.30 (4.35 to 8.05)	20.00 (9.10 to 41.60)	62.70 (19.90 to 99.90)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. Graded according to NCI CTCAE (Version 4.03) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	85	11
Units: Participants	3	4	82	11

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serious Adverse Events (SAEs)

End point title	Number of Participants with Serious Adverse Events (SAEs)

End point description:

A serious adverse event (SAE) is defined as any adverse event (AE) occurring at any dose that:
• Results in death;
• Is life-threatening (ie, in the opinion of the Investigator, the participant is at immediate risk of death from the AE);
• Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay).
• Results in persistent or significant disability/incapacity (a substantial disruption of the participant's ability to conduct normal life functions);
• Is a congenital anomaly/birth defect;
• Constitutes an important medical event.
Graded according to NCI CTCAE (Version 4) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	85	11
Units: Participants	0	2	37	7

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) Leading to Discontinuation

End point title	Number of Participants with Adverse Events (AEs) Leading to Discontinuation

End point description:

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. Graded according to NCI CTCAE (Version 4.03) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	85	11
Units: Participants				
ACY-1215	0	0	13	1
Pomalidomide	0	0	13	1
Dexamethasone	0	0	16	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) Related to Study Drug

End point title	Number of Participants with Adverse Events (AEs) Related to Study Drug

End point description:

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. Graded according to NCI CTCAE (Version 4.03) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death.

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks)

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3	Phase 2 - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	85	11
Units: Participants				
ACY-1215	1	4	63	9
Pomalidomide	3	4	62	11
Dexamethasone	2	3	57	9

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Levels of ACY-1215 and Pomalidomide - Phase 1b

End point title	Plasma Levels of ACY-1215 and Pomalidomide - Phase 1b[10]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1, Cycle 1 Day 2, Cycle 1 Day 8

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Prespecified to be reported for Phase 1b only.

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: ng/L				
ACY-1215 Pomalidomide				

Notes:

[11] - Data not collected

[12] - Data not collected

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Drug Antibodies (ADA) - Phase 1b

End point title	Number of Participants with Anti-Drug Antibodies (ADA) - Phase 1b[13]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1, Cycle 1 Day 2, Cycle 1 Day 8

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Prespecified to be reported for Phase 1b only.

End point values	Phase 1b - ACY-1215 Dose Level 1	Phase 1b - ACY-1215 Dose Level 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Participants				
ACY-1215 Pomalidomide				

Notes:

[14] - Data not collected

[15] - Data not collected

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and Non-Serious AEs were assessed from first dose until 30 days after last dose of study drug (assessed for an average of approximately 55 weeks to a maximum of approximately 456 weeks).

Adverse event reporting additional description:

Serious Adverse Events and Non-Serious Adverse Events represents all participants that received at least 1 dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Phase 1b - ACY-1215 Dose Level 1

Reporting group description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Reporting group title	Phase 2 - ACY-1215 Dose Level 3

Reporting group description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Reporting group title	Phase 2 -ACY-1215 Dose Level 1

Reporting group description:

Participants received 160 mg ACY-1215 and 4 mg pomalidomide daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Reporting group title	Phase 1b - ACY-1215 Dose Level 3

Reporting group description:

Participants received 160 mg ACY-1215 twice daily in combination with 4 mg pomalidomide once daily on Days 1-21 of each 28-day cycle. Participants also received 40 mg (<=75 years) or 20 mg (>75 years) dexamethasone on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Serious adverse events	Phase 1b - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3	Phase 2 -ACY-1215 Dose Level 1
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	7 / 11 (63.64%)	37 / 85 (43.53%)
number of deaths (all causes)	2	3	39
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			

subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory distress			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure congestive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	6 / 85 (7.06%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Septic shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Streptococcal bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			

subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1b - ACY-1215 Dose Level 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Basal cell carcinoma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Delirium				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				

White blood cell count decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femoral neck fracture				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac failure chronic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radiculopathy				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Embolic stroke				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Thrombocytopenia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Pathological fracture				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis bacterial				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia parainfluenzae viral				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Implant site infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypercalcaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour lysis syndrome				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Phase 1b - ACY-1215 Dose Level 1	Phase 2 - ACY-1215 Dose Level 3	Phase 2 -ACY-1215 Dose Level 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	11 / 11 (100.00%)	79 / 85 (92.94%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Flushing			

subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	5 / 85 (5.88%)
occurrences (all)	0	0	5
Hypertension			
subjects affected / exposed	2 / 3 (66.67%)	4 / 11 (36.36%)	2 / 85 (2.35%)
occurrences (all)	4	7	3
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	2	3
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Aortic arteriosclerosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Instillation site pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	4 / 85 (4.71%)
occurrences (all)	0	2	4
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	7 / 85 (8.24%)
occurrences (all)	0	0	8
Chest discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	4 / 85 (4.71%)
occurrences (all)	0	0	4
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	4
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	8 / 11 (72.73%)	49 / 85 (57.65%)
occurrences (all)	2	13	59
Feeling jittery			

subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	5 / 85 (5.88%)
occurrences (all)	0	0	5
Local swelling			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	4 / 85 (4.71%)
occurrences (all)	0	3	4
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	13 / 85 (15.29%)
occurrences (all)	0	2	20
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	18 / 85 (21.18%)
occurrences (all)	0	1	26
Vessel puncture site bruise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	5 / 85 (5.88%)
occurrences (all)	0	0	5
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Acute respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Bronchospasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			

subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	8 / 85 (9.41%)
occurrences (all)	0	2	9
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	4 / 85 (4.71%)
occurrences (all)	0	3	4
Lung infiltration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	4
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	8 / 85 (9.41%)
occurrences (all)	0	1	8
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	9 / 85 (10.59%)
occurrences (all)	0	2	10
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	8 / 85 (9.41%)
occurrences (all)	0	4	8
Cough			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	15 / 85 (17.65%)
occurrences (all)	0	4	21
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	5 / 85 (5.88%)
occurrences (all)	0	1	5
Pulmonary hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	2	3
Sinus congestion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Throat irritation			

subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	2	4
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	3 / 85 (3.53%)
occurrences (all)	2	0	3
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	2 / 85 (2.35%)
occurrences (all)	0	3	2
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	16 / 85 (18.82%)
occurrences (all)	0	4	16
Mood altered			
subjects affected / exposed	1 / 3 (33.33%)	2 / 11 (18.18%)	4 / 85 (4.71%)
occurrences (all)	2	2	4
Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	6 / 85 (7.06%)
occurrences (all)	0	0	6
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 3 (66.67%)	3 / 11 (27.27%)	12 / 85 (14.12%)
occurrences (all)	4	8	27
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	7 / 85 (8.24%)
occurrences (all)	1	0	8
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 3 (66.67%)	0 / 11 (0.00%)	6 / 85 (7.06%)
occurrences (all)	2	0	7
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	4 / 85 (4.71%)
occurrences (all)	1	0	4
Blood cholesterol increased			

subjects affected / exposed	1 / 3 (33.33%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	7 / 85 (8.24%)
occurrences (all)	0	2	10
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Haematocrit decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	3 / 3 (100.00%)	3 / 11 (27.27%)	0 / 85 (0.00%)
occurrences (all)	3	4	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	2	3
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	4 / 11 (36.36%)	6 / 85 (7.06%)
occurrences (all)	3	5	8
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	2	3
White blood cell count decreased			
subjects affected / exposed	2 / 3 (66.67%)	4 / 11 (36.36%)	4 / 85 (4.71%)
occurrences (all)	3	10	8
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	2 / 85 (2.35%)
occurrences (all)	0	2	2
Compression fracture			

subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Periorbital contusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Scar			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Spinal compression fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	3
Cardiac failure congestive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	0 / 85 (0.00%)
occurrences (all)	0	3	0
Sinus tachycardia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences (all)	1	0	1
Tricuspid valve disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Hypoaesthesia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences (all)	0	1	3
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	7 / 85 (8.24%)
occurrences (all)	1	0	7
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	11 / 85 (12.94%)
occurrences (all)	0	1	11
Dizziness postural			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	11 / 85 (12.94%)
occurrences (all)	0	2	12
Balance disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Memory impairment			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	4
VIth nerve paralysis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	10 / 85 (11.76%)
occurrences (all)	0	0	10
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Neuropathy peripheral			

subjects affected / exposed	1 / 3 (33.33%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	1	1	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	31 / 85 (36.47%)
occurrences (all)	0	3	41
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences (all)	0	2	6
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 11 (45.45%)	29 / 85 (34.12%)
occurrences (all)	0	6	59
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	17 / 85 (20.00%)
occurrences (all)	0	1	23
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	4	5
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Ear pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Eye disorders			

Cataract			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	0 / 85 (0.00%)
occurrences (all)	0	3	0
Diplopia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Ectropion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences (all)	0	1	3
Dacryostenosis acquired			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	2	3
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	7 / 85 (8.24%)
occurrences (all)	0	2	8
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	7 / 85 (8.24%)
occurrences (all)	0	1	7
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	6 / 85 (7.06%)
occurrences (all)	0	0	7
Aphthous stomatitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	14 / 85 (16.47%)
occurrences (all)	0	2	16
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	6 / 11 (54.55%)	32 / 85 (37.65%)
occurrences (all)	0	14	47
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	4 / 85 (4.71%)
occurrences (all)	0	2	4
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences (all)	0	1	3
Gastrointestinal disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	3 / 11 (27.27%)	19 / 85 (22.35%)
occurrences (all)	2	3	22
Oral disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Sensitivity of teeth			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Vomiting			

subjects affected / exposed	1 / 3 (33.33%)	1 / 11 (9.09%)	9 / 85 (10.59%)
occurrences (all)	2	2	10
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	5 / 85 (5.88%)
occurrences (all)	0	0	5
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	2 / 11 (18.18%)	2 / 85 (2.35%)
occurrences (all)	1	2	3
Actinic keratosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	2 / 85 (2.35%)
occurrences (all)	0	2	2
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Ecchymosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Erythema multiforme			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Hair growth abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Hair texture abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	2 / 85 (2.35%)
occurrences (all)	0	3	2

Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	10 / 85 (11.76%)
occurrences (all)	0	0	17
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	1	1	1
Skin disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Swelling face			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Renal failure acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	0	2
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Tenosynovitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Bone disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0

Back pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	13 / 85 (15.29%)
occurrences (all)	0	4	15
Arthropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Arthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	13 / 85 (15.29%)
occurrences (all)	0	2	15
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	2 / 85 (2.35%)
occurrences (all)	0	2	2
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	17 / 85 (20.00%)
occurrences (all)	0	3	18
Muscular weakness			
subjects affected / exposed	1 / 3 (33.33%)	2 / 11 (18.18%)	9 / 85 (10.59%)
occurrences (all)	1	2	9
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	4
Musculoskeletal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	4
Osteoarthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Osteoporosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0

Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	9 / 85 (10.59%)
occurrences (all)	0	1	11
Rotator cuff syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	11 / 85 (12.94%)
occurrences (all)	0	2	12
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	4	3
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences (all)	0	1	3
Herpes simplex			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Herpes virus infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	2 / 11 (18.18%)	3 / 85 (3.53%)
occurrences (all)	0	2	4
Localised infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	3 / 85 (3.53%)
occurrences (all)	0	1	3
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	8 / 85 (9.41%)
occurrences (all)	0	0	8
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	3 / 11 (27.27%)	21 / 85 (24.71%)
occurrences (all)	1	9	31
Urinary tract infection			

subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	6 / 85 (7.06%)
occurrences (all)	0	1	7
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	3 / 11 (27.27%)	9 / 85 (10.59%)
occurrences (all)	0	3	10
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	2 / 85 (2.35%)
occurrences (all)	0	1	3
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	4
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	7 / 85 (8.24%)
occurrences (all)	0	1	9
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	1 / 85 (1.18%)
occurrences (all)	0	1	1
Hypermagnesaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 11 (0.00%)	1 / 85 (1.18%)
occurrences (all)	1	0	1
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	4 / 85 (4.71%)
occurrences (all)	0	1	5
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	5 / 85 (5.88%)
occurrences (all)	0	1	5
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 11 (9.09%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	11 / 85 (12.94%)
occurrences (all)	0	0	14

Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	3 / 85 (3.53%)
occurrences (all)	0	0	4
Hyponatraemia			
subjects affected / exposed	2 / 3 (66.67%)	3 / 11 (27.27%)	7 / 85 (8.24%)
occurrences (all)	2	4	9
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 11 (18.18%)	7 / 85 (8.24%)
occurrences (all)	1	7	7
Polydipsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 11 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1b - ACY-1215 Dose Level 3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Aortic arteriosclerosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Instillation site pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Feeling jittery			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Local swelling			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pyrexia			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Vessel puncture site bruise			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Acute respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Bronchospasm			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lung infiltration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Epistaxis			

subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pulmonary hypertension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Throat irritation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Delirium			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Insomnia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mood altered			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood cholesterol increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haematocrit decreased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Compression fracture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Periorbital contusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Scar			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Spinal compression fracture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Procedural pain			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac failure congestive			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinus bradycardia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinus tachycardia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tricuspid valve disease			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dizziness postural			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dizziness			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Memory impairment			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
VIth nerve paralysis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	4		
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Lymphopenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Leukopenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Ear pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Tinnitus subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Eye disorders Cataract subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Diplopia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Dry eye subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Ectropion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Lacrimation increased			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dacryostenosis acquired			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Aphthous stomatitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Gastrointestinal disorder				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Gingival pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Hypoaesthesia oral				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Oral disorder				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Oral pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Sensitivity of teeth				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Vomiting				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Skin and subcutaneous tissue disorders				
Night sweats				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Actinic keratosis				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Alopecia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Ecchymosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Erythema multiforme				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Hair growth abnormal				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Hair texture abnormal				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Hyperhidrosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash maculo-papular				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Skin disorder				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Skin lesion				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Swelling face				

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) Renal failure acute subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 1 / 4 (25.00%) 2		
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0		
Musculoskeletal and connective tissue disorders Bursitis subjects affected / exposed occurrences (all) Tenosynovitis subjects affected / exposed occurrences (all) Bone disorder subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Arthropathy subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Joint swelling	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 		

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Herpes simplex			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Herpes virus infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Localised infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypercalcaemia			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	3		
Hypermagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Polydipsia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2016	Protocol version. Clerical change in Study Personnel. Clarification for Duration of Survival Follow-up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported