Clinical trial results:
Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma

Summary

EudraCT number	2013-001169-18
Trial protocol	FR
Global end of trial date	25 June 2019

Results information

Result version number	v1 (current)
This version publication date	09 July 2020
First version publication date	09 July 2020

Trial information

Trial identification

Sponsor protocol code	2012-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01832727
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen: 20130408

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320-1799
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	25 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1b:
- To determine the maximum tolerated dose (MTD) of oprozomib given orally, once daily, on 2 different schedules: 5 consecutive days every 14 days (bimonthly) or 2 consecutive days every 7 days (weekly) for a 14-day treatment cycle, both schedules given in combination with dexamethasone.
- To evaluate safety and tolerability.

Phase 2:
- To estimate the overall response rate (ORR), defined as the proportion of subjects with the best overall response of stringent complete response (sCR), complete response (CR), near complete response (nCR), very good partial response (VGPR), and partial response (PR) as defined by the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) and modified European Group for Blood and Marrow Transplantation (EBMT) criteria.
- To evaluate safety and tolerability.

Protection of trial subjects:

The study was conducted in accordance with FDA and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and IRB or IEC requirements. This study was approved by a properly constituted IRB/IEC. Before the investigational drug was shipped to the investigator, the investigator or designee provided sponsor with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and ICFs have been reviewed and approved.

The investigator was responsible for notifying his or her IRB/IEC of any significant AEs that are serious and/or unexpected.

Subject medical information obtained as part of this study is confidential and was not disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.
The investigator/institution permits direct access to source data and documents for sponsor, its designee, the FDA, and other applicable regulatory authorities. The access may consist of study-related monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Before any study procedure was implemented, informed consent was documented by the use of a written informed consent form (ICF) approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed ICF was given to the subject or subject's legally authorized representative. The original signed ICF must be maintained by the investigator and available for inspection by sponsor, its designated representative, or regulatory authority at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United States: 58
Worldwide total number of subjects	65
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	33
From 65 to 84 years	30
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 18 centers in the United States and France.

Pre-assignment

Screening details:

Eighty-one subjects were screened; sixteen were not enrolled due to entry criteria violations.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 180 mg 5/14 Schedule (Phase 1b)

Arm description:

Oprozomib 180 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental
Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Arm title	Cohort 210 mg 5/14 Schedule (Phase 1b)

Arm description:

Oprozomib 210 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 5/14 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Arm type	Experimental

Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Arm title	Cohort 150/180 mg 5/14 Schedule (Phase 1b)

Arm description:

Oprozomib 150 mg once daily treatment for 5 consecutive days (days 1, 2, 3, 4, and 5 of a 14-day cycle) followed by a step-up in oprozomib once daily dose to 180 mg starting in cycle 2 and moving forward.
Dexamethasone 20 mg once daily was administered on days 1, 2, 8, and 9 of each 14-day cycle.
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental
Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Arm title	Cohort 210 mg 2/7 Schedule (Phase 1b)

Arm description:

Oprozomib 210 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 2/7 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Arm type	Experimental

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

Arm title	Cohort 240 mg 2/7 Schedule (Phase 1b)

Arm description:

Oprozomib 240 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental
Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Arm title	Cohort 270 mg 2/7 Schedule (Phase 1b)

Arm description:

Oprozomib 270 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

Arm title	Cohort 300 mg 2/7 Schedule (Phase 1b)

Arm description:

Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental
Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Arm title	Cohort 330 mg 2/7 Schedule (Phase 1b)

Arm description:

Oprozomib 330 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental

Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Arm title	Phase 2 300 mg 2/7 Schedule

Arm description:

The Cohort Safety Review Committee (CSRC) determined this dose as the recommended phase 2 dose (RP2D). Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Arm type	Experimental
Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	OPZ , ONX 0912, oprozomib ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib extended release tablets were supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both formulations were administered in a single dose on dosing days. The tablet formulation required multiple tablets to reach each dose on dosing days.

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

Dosage and administration details:

Dexamethasone was administered as 20 mg tablets in strengths of 4 and 6 mg taken orally. If a participant could not tolerate tablets or tablets were unavailable, 20 mg administered intravenously was substituted.

Number of subjects in period 1	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)
Started	9	7	3
Completed	0	0	0
Not completed	9	7	3
Adverse event, serious fatal	-	1	-
Physician decision	1	-	-
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	4	5	1
Study Terminated by Sponsor	-	-	-
Lost to follow-up	-	-	-
Disease Progression	3	-	2

Number of subjects in period 1	Cohort 210 mg 2/7 Schedule (Phase 1b)	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)
Started	4	4	6
Completed	0	0	0
Not completed	4	4	6
Adverse event, serious fatal	-	1	-
Physician decision	1	-	1
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	-	-	1
Study Terminated by Sponsor	-	-	-
Lost to follow-up	1	-	-
Disease Progression	1	3	3

Number of subjects in period 1	Cohort 300 mg 2/7 Schedule (Phase 1b)	Cohort 330 mg 2/7 Schedule (Phase 1b)	Phase 2 300 mg 2/7 Schedule
Started	8	6	18
Completed	0	0	0
Not completed	8	6	18
Adverse event, serious fatal	-	-	-
Physician decision	-	-	-
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	2	1	9
Study Terminated by Sponsor	-	1	1
Lost to follow-up	-	-	-
Disease Progression	6	2	7

Baseline characteristics

Reporting groups

Reporting group title	Cohort 180 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 180 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 210 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 210 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 5/14 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Reporting group title	Cohort 150/180 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 150 mg once daily treatment for 5 consecutive days (days 1, 2, 3, 4, and 5 of a 14-day cycle) followed by a step-up in oprozomib once daily dose to 180 mg starting in cycle 2 and moving forward.
Dexamethasone 20 mg once daily was administered on days 1, 2, 8, and 9 of each 14-day cycle.
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 210 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 210 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 2/7 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Reporting group title	Cohort 240 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 240 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 270 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 270 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 300 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 330 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 330 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for

any reason.

Reporting group title	Phase 2 300 mg 2/7 Schedule

Reporting group description:

The Cohort Safety Review Committee (CSRC) determined this dose as the recommended phase 2 dose (RP2D). Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group values	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)
Number of subjects	9	7	3
Age Categorical Units: Subjects			
Adults (18-64 years)	5	4	2
From 65 - < 75 years	2	3	0
>= 75 years	2	0	1
Age Continuous Units: years			
arithmetic mean	65.8	64.1	67.3
standard deviation	± 13.0	± 4.9	± 6.7
Gender Categorical Units: Subjects			
Female	3	4	1
Male	6	3	2
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	9	7	3
Not reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Black	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	8	7	2
Other	0	0	0
Not reported	0	0	0

Reporting group values	Cohort 210 mg 2/7 Schedule (Phase 1b)	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)
Number of subjects	4	4	6
Age Categorical Units: Subjects			
Adults (18-64 years)	1	4	2
From 65 - < 75 years	2	0	3
>= 75 years	1	0	1

Age Continuous			
Units: years			
arithmetic mean	68.5	53.8	66.7
standard deviation	± 12.0	± 8.6	± 9.1
Gender Categorical			
Units: Subjects			
Female	2	1	2
Male	2	3	4
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	4	2	6
Not reported	0	1	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	3	2	4
Other	0	1	0
Not reported	0	0	0

Reporting group values	Cohort 300 mg 2/7 Schedule (Phase 1b)	Cohort 330 mg 2/7 Schedule (Phase 1b)	Phase 2 300 mg 2/7 Schedule
Number of subjects	8	6	18
Age Categorical			
Units: Subjects			
Adults (18-64 years)	4	5	6
From 65 - < 75 years	3	0	7
>= 75 years	1	1	5
Age Continuous			
Units: years			
arithmetic mean	65.6	59.7	68.9
standard deviation	± 10.4	± 9.9	± 8.0
Gender Categorical			
Units: Subjects			
Female	3	2	9
Male	5	4	9
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	8	5	11
Not reported	0	0	7
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black	1	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	7	4	10

Other	0	1	0
Not reported	0	0	7

Reporting group values	Total		
Number of subjects	65		
Age Categorical Units: Subjects			
Adults (18-64 years)	33		
From 65 - < 75 years	20		
>= 75 years	12		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender Categorical Units: Subjects			
Female	27		
Male	38		
Ethnicity Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	55		
Not reported	8		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Black	8		
Native Hawaiian or Other Pacific Islander	0		
White	47		
Other	2		
Not reported	7		

End points

End points reporting groups

Reporting group title	Cohort 180 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 180 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 210 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 210 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 5/14 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Reporting group title	Cohort 150/180 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 150 mg once daily treatment for 5 consecutive days (days 1, 2, 3, 4, and 5 of a 14-day cycle) followed by a step-up in oprozomib once daily dose to 180 mg starting in cycle 2 and moving forward.
Dexamethasone 20 mg once daily was administered on days 1, 2, 8, and 9 of each 14-day cycle.
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 210 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 210 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 2/7 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Reporting group title	Cohort 240 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 240 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 270 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 270 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 300 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 330 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 330 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for

any reason.

Reporting group title	Phase 2 300 mg 2/7 Schedule

Reporting group description:

The Cohort Safety Review Committee (CSRC) determined this dose as the recommended phase 2 dose (RP2D). Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Subject analysis set title	180 mg Oprozomib Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 180 mg oprozomib tablets.

Subject analysis set title	210 mg Oprozomib Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 210 mg oprozomib tablets.

Subject analysis set title	240 mg Oprozomib Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 240 mg oprozomib tablets.

Subject analysis set title	270 mg Oprozomib Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 270 mg oprozomib tablets.

Subject analysis set title	300 mg Oprozomib Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 300 mg oprozomib tablets.

Subject analysis set title	150 mg Oprozomib ER Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 150 mg extended release oprozomib tablets.

Subject analysis set title	300 mg Oprozomib ER Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 300 mg extended release oprozomib tablets.

Subject analysis set title	330 mg Oprozomib ER Tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were administered 330 mg extended release oprozomib tablets.

Primary: Participants With Dose-Limiting Toxicities (DLT)

End point title	Participants With Dose-Limiting Toxicities (DLT)[1]

End point description:

Toxicities (graded per the Common Terminology Criteria for Adverse Events v 4.03) were considered DLTs if judged by the investigator to be related to oprozomib and occurred in the first 14 days of treatment, with treatment at the dose to be studied (i.e., Cycle 1 for continuous dosing or Cycle 2 for step-up dosing). A DLT was categorized as nonhematologic or hematologic.
Examples include:
• Any ≥ Grade 3 nonhematologic AE, with exceptions or qualifications such as Grade 3 nausea, vomiting, diarrhea, or constipation were considered a DLT only if lasting for > 7 days despite optimal supportive care
• Grade 3 fatigue lasting > 14 days
• Grade 4 neutropenia: absolute neutrophil count (ANC) < 500 cells/mcL lasting ≥ 7 days
• Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for over 1 hour with ≥Grade 3 neutropenia (ANC < 1000 cells/mcL)

• Grade 3/4 thrombocytopenia
• Others specified in the protocol

End point type	Primary

End point timeframe:

Day 1 to Day 14 (Cycle 1) for continuous dosing and Day 15 to Day 28 (Cycle 2) for step-up dosing

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical reporting of safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 2/7 Schedule (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	7	3	4
Units: participants				
Participants reporting >=1 DLT	0	3	1	0
Mental status changes	0	0	1	0
Alanine aminotransferase increased	0	1	0	0
Aspartate aminotransferase increased	0	1	0	0
Hypertension	0	1	0	0
Subarachnoid haemorrhage	0	1	0	0
Thrombocytopenia	0	1	0	0
Anaemia	0	0	0	0
Nausea	0	0	0	0
Upper respiratory tract infection	0	0	0	0
Vomiting	0	0	0	0
Pain in jaw	0	0	0	0

End point values	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)	Cohort 300 mg 2/7 Schedule (Phase 1b)	Cohort 330 mg 2/7 Schedule (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	8	6
Units: participants				
Participants reporting >=1 DLT	0	2	0	2
Mental status changes	0	0	0	0
Alanine aminotransferase increased	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0
Hypertension	0	0	0	0
Subarachnoid haemorrhage	0	0	0	0
Thrombocytopenia	0	1	0	0
Anaemia	0	0	0	0
Nausea	0	0	0	1
Upper respiratory tract infection	0	0	0	1
Vomiting	0	0	0	1
Pain in jaw	0	1	0	0

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: participants				
Participants reporting >=1 DLT	1			
Mental status changes	0			
Alanine aminotransferase increased	0			
Aspartate aminotransferase increased	0			
Hypertension	0			
Subarachnoid haemorrhage	0			
Thrombocytopenia	0			
Anaemia	1			
Nausea	0			
Upper respiratory tract infection	0			
Vomiting	0			
Pain in jaw	0			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Treatment-Emergent Adverse Events (TEAEs) During Phase 1b and 2

End point title	Participants With Treatment-Emergent Adverse Events (TEAEs) During Phase 1b and 2[2]

End point description:

AE defined as any untoward medical occurrence in a clinical trial subject. Treatment-emergent adverse events were defined as adverse events that start on or after the first day of study treatment and within 30 days of the last day of study treatment. An adverse event that was present before the first administration of study treatment and subsequently worsens in severity during treatment was also considered to be treatment-emergent.
Serious AE defined as AE that is fatal, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or other significant medical hazard. Severity of AEs assessed according to Common Terminology Criteria for Adverse Events (CTCAE, v4.03) based on general guideline:
Grade 1: Mild;
Grade 2: Moderate;
Grade 3: Severe;
Grade 4: Life-threatening or disabling;
Grade 5: Death related to AE

IP=investigational product

End point type	Primary

End point timeframe:

Day 1 up to Week 282

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: Statistical reporting of safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 2/7 Schedule (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	7	3	4
Units: participants				
>=1 TEAE	9	7	3	4
Grade >=3 (severe)	8	5	2	3
Serious AE	4	2	2	2
Leading to discontinuation of IP	4	6	1	0
Fatal AE	0	1	0	0

End point values	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)	Cohort 300 mg 2/7 Schedule (Phase 1b)	Cohort 330 mg 2/7 Schedule (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	8	6
Units: participants				
>=1 TEAE	4	6	8	6
Grade >=3 (severe)	3	5	6	5
Serious AE	1	1	3	0
Leading to discontinuation of IP	1	1	2	1
Fatal AE	1	0	0	0

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: participants				
>=1 TEAE	18			
Grade >=3 (severe)	16			
Serious AE	9			
Leading to discontinuation of IP	11			
Fatal AE	0			

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Treatment-Related, Treatment-Emergent Adverse Events (TEAEs) During Phase 1b and 2

End point title	Participants With Treatment-Related, Treatment-Emergent Adverse Events (TEAEs) During Phase 1b and 2[3]

End point description:

AE defined as any untoward medical occurrence in a clinical trial participant. TEAEs were defined as AEs that start on or after the first day of study treatment and within 30 days of the last day of study treatment. An AE that was present before the first administration of study treatment and subsequently worsens in severity during treatment was also considered a TEAE.
Investigator assessed AEs for relatedness to study drug. Serious AE defined as AE that is fatal, life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or other significant medical hazard. Severity of AEs assessed according to Common Terminology Criteria for Adverse Events (CTCAE, v4.03) based on the general guideline: Grade 1: Mild;
Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening or disabling; Grade 5: Death related to AE.

IP=investigational product

End point type	Primary

End point timeframe:

Day 1 up to Week 282

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical reporting of safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 2/7 Schedule (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	7	3	4
Units: participants				
>=1 related TEAE	9	7	3	4
Grade >=3 (severe)	8	5	2	2
Serious AE	3	2	0	1
Leading to discontinuation of IP	3	6	0	0
Fatal AE	0	1	0	0

End point values	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)	Cohort 300 mg 2/7 Schedule (Phase 1b)	Cohort 330 mg 2/7 Schedule (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	8	6
Units: participants				
>=1 related TEAE	4	6	8	6
Grade >=3 (severe)	2	2	4	3
Serious AE	0	0	2	0
Leading to discontinuation of IP	1	1	1	1
Fatal AE	0	0	0	0

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			

Units: participants				
>=1 related TEAE	18			
Grade >=3 (severe)	14			
Serious AE	3			
Leading to discontinuation of IP	7			
Fatal AE	0			

Statistical analyses

No statistical analyses for this end point

Primary: Best Overall Response in Phase 2 as Assessed by Investigator

End point title	Best Overall Response in Phase 2 as Assessed by

End point description:

Disease response and progression were determined using the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC), except for minimal response (MR) and near complete response (nCR) which was based on the European Group for Blood and Marrow Transplantation (EBMT) criteria. Evaluations reported were assessed by the investigator for participants in Phase 2.

End point type	Primary

End point timeframe:

Screening: Day 14 to Day -1; During study: Day 1 up to 13.16 months

Notes:

[4] - 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: Formal statistics were not performed for the single arm reported in Phase 2

[5] - 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: The protocol specified that efficacy endpoints would be reported for the phase 2 treatment arm only.

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: participants				
Stringent Complete Response (sCR)	0			
Complete Response (CR)	1			
Near Complete Response (nCR)	0			
Very Good Partial Response (VGPR)	2			
Partial Response (PR)	9			
Minimal Response (MR)	1			
Stable Disease (SD)	2			
Progressive Disease (PD)	1			
Not Evaluable (NE)	2			
Unknown	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Achieved an Overall Response As Assessed by Investigator During Phase 2

End point title	Percentage of Participants Who Achieved an Overall Response As Assessed by Investigator During Phase 2[6][7]

End point description:

The overall response rate (ORR) was defined as the percentage of participants with the best overall response of stringent complete response (sCR), complete response (CR), near complete response (nCR), very good partial response (VGPR), and partial response (PR) as defined by the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) and modified European Group for Blood and Marrow Transplantation (EBMT) criteria.

End point type	Primary

End point timeframe:

Day 14 to Day -1; During study: Day 1 up to 13.16 months

Notes:

[6] - 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: Formal statistics were not performed for the single arm reported in Phase 2

[7] - 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: The protocol specified that efficacy endpoints would be reported for the phase 2 treatment arm only.

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 95%)	66.7 (41.0 to 86.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Oprozomib, Tablet and ER Formulation: Time to Maximum Serum Concentration on Cycle 1, Day 1

End point title	PK Parameter for Oprozomib, Tablet and ER Formulation: Time to Maximum Serum Concentration on Cycle 1, Day 1

End point description:

PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2.
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2.
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2.

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	4	6
Units: hour				
median (full range (min-max))	1.0 (0.50 to 2.0)	1.1 (0.50 to 6.0)	1.0 (0.98 to 2.0)	1.0 (0.50 to 2.0)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	3	19	6
Units: hour				
median (full range (min-max))	2.0 (1.0 to 3.9)	2.0 (1.1 to 4.0)	1.0 (0.50 to 2.0)	1.5 (0.47 to 4.0)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Oprozomib, Tablet and ER Formulation: Maximum Serum Concentration (Cmax) on Cycle 1, Day 1

End point title	PK Parameter for Oprozomib, Tablet and ER Formulation: Maximum Serum Concentration (Cmax) on Cycle 1, Day 1

End point description:

PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	4	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)	633 (± 192.1)	754 (± 91.7)	841 (± 73.8)	906 (± 69.3)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	3	19	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)	881 (± 37.8)	672 (± 54.5)	785 (± 63.7)	578 (± 80.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Oprozomib, Tablet and ER Formulation: Area Under the Curve at the Last Quantifiable Concentration (AUClast) on Cycle 1, Day 1

End point title	PK Parameter for Oprozomib, Tablet and ER Formulation: Area Under the Curve at the Last Quantifiable Concentration (AUClast) on Cycle 1, Day 1

End point description:

The area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUClast) was estimated using the linear trapezoidal method.

PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	4	6
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	1140 (± 197.4)	1770 (± 104.7)	2170 (± 51.8)	1900 (± 68.9)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	3	19	6
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	2530 (± 63.4)	1690 (± 16.1)	1740 (± 70.3)	1690 (± 70.8)

Statistical analyses

No statistical analyses for this end point

Secondary: PK for Oprozomib, Tablet and ER Formulation: Area Under the Curve From Time 0 to Infinity (AUCinf) on Cycle 1 Day 1

End point title	PK for Oprozomib, Tablet and ER Formulation: Area Under the Curve From Time 0 to Infinity (AUCinf) on Cycle 1 Day 1

End point description:

The area under the plasma concentration-curve from time 0 to time infinity (AUCinf) was estimated using the linear trapezoidal method.
PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2

9999 = Not reported

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	6	4	4
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	947 (± 229.7)	1600 (± 127.2)	2180 (± 51.6)	1970 (± 88.8)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	1	15	4
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	2550 (± 63.5)	9999 (± 9999)	1900 (± 77.7)	2150 (± 27.6)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Oprozomib, Tablet and ER Formulation: Terminal Half-Life (t1/2,z) on Cycle 1, Day 1

End point title	PK Parameter for Oprozomib, Tablet and ER Formulation: Terminal Half-Life (t1/2,z) on Cycle 1, Day 1

End point description:

PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2

9999 = Not reported

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	6	4	4
Units: hour				
geometric mean (geometric coefficient of variation)	0.962 (± 40.6)	0.573 (± 29.4)	0.970 (± 79.2)	0.850 (± 29.5)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	1	15	4

Units: hour				
geometric mean (geometric coefficient of variation)	1.36 (± 80.1)	9999 (± 9999)	0.710 (± 40.7)	0.805 (± 40.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Oprozomib, Tablet and ER Formulation: Apparent Drug Clearance After Oral Administration (CL/F) on Cycle 1, Day 1

End point title	PK Parameter for Oprozomib, Tablet and ER Formulation: Apparent Drug Clearance After Oral Administration (CL/F) on Cycle 1, Day 1

End point description:

The apparent drug clearance after oral administration (CL/F) was calculated as the dose divided by AUCinf.

PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2

9999 = Not reported

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	6	4	4
Units: mL/hour				
geometric mean (geometric coefficient of variation)	190000 (± 229.7)	131000 (± 127.2)	110000 (± 51.6)	137000 (± 88.8)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	1	15	4
Units: mL/hour				
geometric mean (geometric coefficient of variation)	118000 (± 63.5)	9999 (± 9999)	157000 (± 77.7)	153000 (± 27.6)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Oprozomib, Tablet and ER Formulation: Apparent Volume of Distribution After Oral Administration (Vz/F) on Cycle 1, Day 1

End point title	PK Parameter for Oprozomib, Tablet and ER Formulation: Apparent Volume of Distribution After Oral Administration (Vz/F) on Cycle 1, Day 1

End point description:

The apparent volume of distribution after oral administration (Vz/F) calculated as the dose divided by AUCinf times λz, where λz was the first-order terminal rate constant estimated via linear regression of the terminal log-linear phase.

PK samples obtained on the following schedule:
Phase 1b Continuous Dosing, Cycles 1 and 2: Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 8 hours post-dose plus pre-dose on Day 2
Phase 1b Step-up Dosing, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus pre-dose on Day 2
Phase 2, Day 1: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, 6, and 7 hours post-dose plus predose on Day 2

9999 = Not reported

End point type	Secondary

End point timeframe:

Day 1

End point values	180 mg Oprozomib Tablet	210 mg Oprozomib Tablet	240 mg Oprozomib Tablet	270 mg Oprozomib Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	6	4	4
Units: mL				
geometric mean (geometric coefficient of variation)	264000 (± 235.6)	108000 (± 106.7)	154000 (± 79.5)	168000 (± 138.9)

End point values	300 mg Oprozomib Tablet	150 mg Oprozomib ER Tablet	300 mg Oprozomib ER Tablet	330 mg Oprozomib ER Tablet
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	1	15	4
Units: mL				
geometric mean (geometric coefficient of variation)	231000 (± 54.7)	9999 (± 9999)	161000 (± 69.0)	178000 (± 44.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved a Clinical Benefit Response As Assessed by Investigator During Phase 2

End point title	Percentage of Participants Who Achieved a Clinical Benefit Response As Assessed by Investigator During Phase 2[8]

End point description:

The clinical benefit rate (CBR) was defined as Overall Response Rate (ORR) plus Minimal Response (MR) as defined by the European Group for Blood and Marrow Transplantation (EBMT) criteria.

End point type	Secondary

End point timeframe:

Day 14 to Day -1; During study: Day 1 up to 13.16 months

Notes:

[8] - 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: The protocol specified that efficacy endpoints would be reported for the phase 2 treatment arm only.

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 95%)	72.2 (46.5 to 90.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Duration of Response (DOR) as Assessed by Investigator During Phase 2

End point title	Kaplan-Meier Estimates for Duration of Response (DOR) as Assessed by Investigator During Phase 2[9]

End point description:

Duration of response was defined as the time from first evidence of partial response (PR) or better (i.e. best overall response) to confirmation of disease progression or death due to any cause. Durations were calculated for responders only.
Medians and percentiles were estimated using the Kaplan-Meier method.
95% confidence intervals for medians and percentiles were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

9999 = not estimable.

End point type	Secondary

End point timeframe:

Day 1 up to 13.16 months

Notes:

[9] - 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: The protocol specified that efficacy endpoints would be reported for the phase 2 treatment arm only.

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)	9999 (6.8 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Progression-free Survival (PFS) as Assessed by Investigator During Phase 2

End point title	Kaplan-Meier Estimates for Progression-free Survival (PFS) as Assessed by Investigator During Phase 2[10]

End point description:

Progression-free survival (PFS) was defined as number of months between start of treatment and first evidence of documented disease progression or death (due to any cause), whichever occurs first. Disease progression was determined using IMWG-URC per investigator. The duration of PFS was right–censored for participants who met 1 of the following conditions:
• 1) starting a new anticancer therapy before documentation of disease progression or death;
• 2) death or disease progression immediately after more than 1 consecutively missed disease assessment visit or;
• 3) alive without documentation of disease progression before the data cutoff date.

95% CIs for medians were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

9999 = not estimable

End point type	Secondary

End point timeframe:

Day 1 up to 14.1 months

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: The protocol specified that efficacy endpoints would be reported for the phase 2 treatment arm only.

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)	12.2 (3.5 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate for Time to Progression (TTP) as Assessed by Investigator During Phase 2

End point title	Kaplan-Meier Estimate for Time to Progression (TTP) as Assessed by Investigator During Phase 2[11]

End point description:

Time to progression (TTP) was defined as the number of months between the start of treatment to the first documentation of disease progression.
Disease progression was determined using IMWG-URC as
assessed by the investigator. The same censoring rules, except for death, as in analysis of PFS were applied in the calculation of TTP.
Participants who died prior to progressive disease were censored at the date of last evaluable response assessment.

9999 = not estimable

End point type	Secondary

End point timeframe:

Day 1 up to 14.1 months

Notes:

[11] - 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: The protocol specified that efficacy endpoints would be reported for the phase 2 treatment arm only.

End point values	Phase 2 300 mg 2/7 Schedule			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)	12.2 (3.5 to 9999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events - Day 1 up to Week 282

Adverse event reporting additional description:

Mortality - Death that occurred from the first dose of study drug until the end of study. Adverse Events - From the first dose of study drug until 30 days after the last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Cohort 180 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 180 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 210 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 210 mg treatment once daily for 5 consecutive days bimonthly (days 1, 2, 3, 4, and 5 of a 14-day cycle) with 20 mg dexamethasone once daily on days 1, 2, 8, and 9 (referred to as the 5/14 schedule).
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 5/14 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Reporting group title	Cohort 210 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 210 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
This was the first cohort to enroll participants into the 2/7 schedule. The Cohort Safety Review Committee (CSRC) reviewed safety data and made dose adjustments for oprozomib in 30 mg increments for all cohorts.

Reporting group title	Cohort 240 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 240 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 270 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 270 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 300 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 330 mg 2/7 Schedule (Phase 1b)

Reporting group description:

Oprozomib 330 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Cohort 150/180 mg 5/14 Schedule (Phase 1b)

Reporting group description:

Oprozomib 150 mg once daily treatment for 5 consecutive days (days 1, 2, 3, 4, and 5 of a 14-day cycle) followed by a step-up in oprozomib once daily dose to 180 mg starting in cycle 2 and moving forward.
Dexamethasone 20 mg once daily was administered on days 1, 2, 8, and 9 of each 14-day cycle.
Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Reporting group title	Phase 2 300 mg 2/7 Schedule

Reporting group description:

The Cohort Safety Review Committee (CSRC) determined this dose as the recommended phase 2 dose (RP2D). Oprozomib 300 mg once daily on Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone once daily on Days 1, 2, 8, and 9 of a 14-day cycle.

Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Serious adverse events	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 2/7 Schedule (Phase 1b)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	2 / 7 (28.57%)	2 / 4 (50.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (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
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
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, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone lesion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Meningitis aseptic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Pneumonia			

subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Spinal cord infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (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
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
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			
Dehydration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)	Cohort 300 mg 2/7 Schedule (Phase 1b)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	3 / 8 (37.50%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Oesophagitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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			
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Musculoskeletal and connective tissue disorders			
Bone lesion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (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
Infections and infestations			
Clostridium difficile infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Meningitis aseptic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Spinal cord infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
Tumour lysis syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (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

Serious adverse events	Cohort 330 mg 2/7 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)	Phase 2 300 mg 2/7 Schedule
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	9 / 18 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Thrombocytopenia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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			
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (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
Meningitis aseptic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (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
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	3 / 18 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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

Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (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

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

Non-serious adverse events	Cohort 180 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 5/14 Schedule (Phase 1b)	Cohort 210 mg 2/7 Schedule (Phase 1b)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	7 / 7 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Squamous cell carcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Haematoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	3 / 9 (33.33%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	3	3	1
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Orthostatic hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Post thrombotic syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Joint surgery			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Medical device implantation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	2 / 9 (22.22%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Facial pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	6 / 9 (66.67%)	4 / 7 (57.14%)	2 / 4 (50.00%)
occurrences (all)	13	5	8
Feeling abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Feeling jittery			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nodule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	1	1	3
Pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			

Balanoposthitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Breast disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Erectile dysfunction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Uterine prolapse			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vaginal prolapse			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Dysphonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	2 / 9 (22.22%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	4	1	1
Dyspnoea exertional			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			

subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	2 / 9 (22.22%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Hypoxia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Orthopnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhonchi			

subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Sneezing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Bruxism			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Disorientation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Irritability			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Mental disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Mental status changes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Thinking abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Aspartate aminotransferase decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Blood creatinine decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	3 / 9 (33.33%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Blood pressure abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood urea decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood uric acid decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	0	2	2
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	2 / 9 (22.22%)	2 / 7 (28.57%)	0 / 4 (0.00%)
occurrences (all)	3	5	0
Protein total increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			

subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
White blood cell count increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Animal scratch			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Concussion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Infusion related reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Thermal burn			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arrhythmia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Bundle branch block right			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diastolic dysfunction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	3 / 9 (33.33%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Dysgeusia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
Head discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	2 / 4 (50.00%)
occurrences (all)	1	2	2
Hypoaesthesia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Presyncope			

subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Somnolence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 9 (33.33%)	2 / 7 (28.57%)	1 / 4 (25.00%)
occurrences (all)	17	2	1
Leukopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	9	1	2
Microcytic anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	1 / 4 (25.00%)
occurrences (all)	8	2	2
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear congestion			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Middle ear effusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Otorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Visual impairment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	2 / 9 (22.22%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Abdominal pain upper			
subjects affected / exposed	3 / 9 (33.33%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Abdominal rigidity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Anal incontinence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	2 / 9 (22.22%)	2 / 7 (28.57%)	2 / 4 (50.00%)
occurrences (all)	3	2	2
Dental caries			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	8 / 9 (88.89%)	6 / 7 (85.71%)	4 / 4 (100.00%)
occurrences (all)	26	23	21
Diverticulum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	2 / 9 (22.22%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	3 / 9 (33.33%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Eructation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Faeces soft			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia oral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ileus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Large intestine polyp			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lip haematoma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	8 / 9 (88.89%)	7 / 7 (100.00%)	4 / 4 (100.00%)
occurrences (all)	26	22	23
Oral disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Periodontal disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	6 / 9 (66.67%)	5 / 7 (71.43%)	4 / 4 (100.00%)
occurrences (all)	16	19	11
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Angioedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Chronic papillomatous dermatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Drug eruption			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Miliaria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nail ridging			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Night sweats			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Onychomadesis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nocturia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Renal failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urinary hesitation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Exostosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Muscular weakness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Pain in jaw			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Clostridium difficile infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Genital herpes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haemophilus infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Tinea cruris			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			

subjects affected / exposed	5 / 9 (55.56%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	5	1	0
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Diabetes mellitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fluid overload			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	6	2	2
Hyperkalaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 7 (14.29%)	1 / 4 (25.00%)
occurrences (all)	7	1	1
Hypocalcaemia			
subjects affected / exposed	3 / 9 (33.33%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	7	1	0
Hypoglycaemia			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	4 / 9 (44.44%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	6	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 7 (14.29%)	0 / 4 (0.00%)
occurrences (all)	6	2	0
Hypophosphataemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hypovolaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lactic acidosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Malnutrition			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 240 mg 2/7 Schedule (Phase 1b)	Cohort 270 mg 2/7 Schedule (Phase 1b)	Cohort 300 mg 2/7 Schedule (Phase 1b)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	6 / 6 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Squamous cell carcinoma			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	1 / 8 (12.50%)
occurrences (all)	2	4	1
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Phlebitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Post thrombotic syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Venous thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Joint surgery			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Medical device implantation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Facial pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)	4 / 6 (66.67%)	7 / 8 (87.50%)
occurrences (all)	3	9	21
Feeling abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Feeling jittery			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	2	4	0
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nodule			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	2	1	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			

Balanoposthitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Breast disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Erectile dysfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Uterine prolapse			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vaginal prolapse			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	3	3	1
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Dyspnoea exertional			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Haemoptysis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Oropharyngeal pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Orthopnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rhonchi			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Bruxism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Disorientation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	1	3	4
Irritability			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Mental disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Mental status changes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thinking abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	1	1	2
Aspartate aminotransferase decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Blood alkaline phosphatase decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Blood creatinine decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Blood pressure abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood urea decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood uric acid decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Neutrophil count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Platelet count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Protein total increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			

subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Animal scratch			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Concussion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Thermal burn			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Arrhythmia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Bundle branch block right			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diastolic dysfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Pericardial effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	1	1	3
Dysgeusia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	3 / 8 (37.50%)
occurrences (all)	4	1	4
Head discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	3 / 8 (37.50%)
occurrences (all)	1	2	10
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Presyncope			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	5 / 8 (62.50%)
occurrences (all)	1	0	9
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Microcytic anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	3 / 8 (37.50%)
occurrences (all)	2	7	7
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear congestion			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ear discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Middle ear effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Otorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Visual impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Abdominal distension			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	36
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Abdominal rigidity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Anal incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	4 / 8 (50.00%)
occurrences (all)	12	1	15
Dental caries			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	6 / 6 (100.00%)	7 / 8 (87.50%)
occurrences (all)	13	53	76
Diverticulum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	5	1	10
Eructation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Faeces soft			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	3 / 8 (37.50%)
occurrences (all)	0	3	4
Gingival bleeding			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Large intestine polyp			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Lip haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	5 / 6 (83.33%)	7 / 8 (87.50%)
occurrences (all)	26	16	62
Oral disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Periodontal disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 4 (75.00%)	2 / 6 (33.33%)	2 / 8 (25.00%)
occurrences (all)	3	25	6
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Angioedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic papillomatous dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Drug eruption			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Ecchymosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Miliaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nail ridging			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Night sweats			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	6
Onychomadesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nocturia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary hesitation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
Bone pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Exostosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Joint stiffness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Joint swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Limb discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	5
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	3
Myalgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Osteonecrosis of jaw			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	3
Pain in jaw			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Clostridium difficile infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Genital herpes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haemophilus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tinea cruris			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	3 / 8 (37.50%)
occurrences (all)	1	6	3
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			

subjects affected / exposed	3 / 4 (75.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	32	0	2
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Fluid overload			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	2
Hyperglycaemia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	6	1	2
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypermagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	2
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Hypoglycaemia			

subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	0 / 8 (0.00%)
occurrences (all)	2	11	0
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypovolaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lactic acidosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Malnutrition			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 330 mg 2/7 Schedule (Phase 1b)	Cohort 150/180 mg 5/14 Schedule (Phase 1b)	Phase 2 300 mg 2/7 Schedule
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 3 (100.00%)	18 / 18 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	5
Squamous cell carcinoma			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Deep vein thrombosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	5	5	1
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Orthostatic hypotension			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Phlebitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Post thrombotic syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Venous thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Joint surgery			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Medical device implantation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	8 / 18 (44.44%)
occurrences (all)	1	0	32
Chest discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	2 / 6 (33.33%)	2 / 3 (66.67%)	3 / 18 (16.67%)
occurrences (all)	4	3	4
Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Facial pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	6 / 6 (100.00%)	2 / 3 (66.67%)	7 / 18 (38.89%)
occurrences (all)	12	4	16
Feeling abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Feeling jittery			

subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nodule			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	5 / 18 (27.78%)
occurrences (all)	2	2	5
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	5 / 18 (27.78%)
occurrences (all)	0	8	7
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			

Balanoposthitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Breast disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Erectile dysfunction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Uterine prolapse			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vaginal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Vaginal prolapse			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	6 / 18 (33.33%)
occurrences (all)	0	2	9
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	2 / 18 (11.11%)
occurrences (all)	3	2	4
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	5
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Orthopnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rhonchi			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	4
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Bruxism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Disorientation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	4 / 18 (22.22%)
occurrences (all)	3	0	8
Irritability			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Mental disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Mental status changes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Thinking abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Aspartate aminotransferase decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood creatinine decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood phosphorus increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Blood pressure abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood urea decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood uric acid decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Protein total increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	3 / 18 (16.67%)
occurrences (all)	1	0	4
White blood cell count decreased			

subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Animal scratch			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Concussion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Thermal burn			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Arrhythmia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Bundle branch block right			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Diastolic dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Ventricular extrasystoles			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	5	0	7
Dysgeusia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	4 / 18 (22.22%)
occurrences (all)	67	0	4
Head discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	6 / 18 (33.33%)
occurrences (all)	2	0	9
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Presyncope			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 6 (50.00%)	1 / 3 (33.33%)	8 / 18 (44.44%)
occurrences (all)	7	1	21
Leukopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Microcytic anaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	4 / 18 (22.22%)
occurrences (all)	2	1	11
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Ear congestion			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Middle ear effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Otorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	2 / 18 (11.11%)
occurrences (all)	0	1	5
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	15
Eye disorders			
Cataract			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	5
Visual impairment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vitreous floaters			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Abdominal distension			

subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	7 / 18 (38.89%)
occurrences (all)	24	0	11
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	6 / 18 (33.33%)
occurrences (all)	1	0	15
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	4 / 18 (22.22%)
occurrences (all)	1	0	7
Abdominal rigidity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Anal incontinence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	5 / 6 (83.33%)	1 / 3 (33.33%)	10 / 18 (55.56%)
occurrences (all)	16	1	26
Dental caries			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	5 / 6 (83.33%)	2 / 3 (66.67%)	14 / 18 (77.78%)
occurrences (all)	35	4	71
Diverticulum			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	6 / 18 (33.33%)
occurrences (all)	0	0	19
Eructation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Faeces soft			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	5
Gingival bleeding			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ileus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Large intestine polyp			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Lip haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	6 / 6 (100.00%)	3 / 3 (100.00%)	12 / 18 (66.67%)
occurrences (all)	67	5	56
Oral disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Periodontal disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Retching			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	5 / 6 (83.33%)	3 / 3 (100.00%)	8 / 18 (44.44%)
occurrences (all)	11	5	22
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Actinic keratosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Angioedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blister			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Chronic papillomatous dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Drug eruption			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Ecchymosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Miliaria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nail ridging			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Night sweats			

subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	7
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nocturia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1

Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Urinary hesitation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Urinary incontinence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	0	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Arthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Exostosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Limb discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Muscle spasms			

subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	6 / 18 (33.33%)
occurrences (all)	0	1	11
Muscular weakness			
subjects affected / exposed	3 / 6 (50.00%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	7	2	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	3	0	2
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Pain in jaw			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Clostridium difficile infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Diverticulitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Genital herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemophilus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Herpes zoster			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Hordeolum			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tinea cruris			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 6 (83.33%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	9	0	1
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	4
Decreased appetite			

subjects affected / exposed	2 / 6 (33.33%)	2 / 3 (66.67%)	5 / 18 (27.78%)
occurrences (all)	2	3	5
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	2	1	2
Diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Fluid overload			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Hypocalcaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Hypoglycaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	2 / 18 (11.11%)
occurrences (all)	2	1	3
Hypomagnesaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	3	0	3
Hyponatraemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	5
Hypophosphataemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Hypovolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lactic acidosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Malnutrition			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2013	Study 2012-001 was amended to implement a new starting dose for Oprozomib Tablets for both dosing schedules based on dose-escalation data from ongoing Study 2011-001. Other key changes: 1. Global change: Starting dose of 150 mg was changed to 210 mg for both oprozomib dosing schedules. This update was made based on dose-escalation data from ongoing Study 2011-001 from both tablet and product-in-capsule (PIC) formulations. 2. Global change: Changed units for absolute neutrophil count (ANC) and platelet counts from [value] *10^9/L to standard units, [value] cells/mcL. 3. Study Synopsis (Test Product, Dose, and Mode of Administration): Removed specific dexamethasone oral tablet strengths (4 mg and 6 mg). This text did not appear in the protocol body. 4. Section 1.4.1: Added dose rationale for 210 mg starting dose of Oprozomib Tablets based on preliminary safety results from Study 2011-001, PK data demonstrating comparable exposures between the tablet and capsule, and rationale for the combination of oprozomib with low-dose dexamethasone as a means to reduce gastrointestinal (GI) toxicity. 5. Section 3.4, Appendix A and Appendix B (footnote 1): Added that subjects continuing on study treatment and whose disease has not progressed 1 year after starting study treatment will reduce the frequency of their visits (on Day 1 of their next scheduled cycle) to every 4 weeks instead of every 2 weeks, with adequate drug supply for 2 cycles of treatment. Also clarified that disease response will be assessed every 8 weeks (4 cycles) after 1 year on therapy. 6. Section 4.1: Clarified in Inclusion Criterion #5 that bilirubin must be . 1.5 times the upper limit of normal (ULN) in the absence of Gilbert's disease or hemolysis. 7. Section 4.2: Clarified in Exclusion Criterion #3 that glucocorticoid therapy within 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent is not allowed. OTHER CHANGES
25 June 2013	Study 2012-001 was amended to incorporate FDA requested changes/additions, specifically with regard to the definition of dose-limiting toxicities as applied to the Phase 1b component of the study and the incorporation of specific guidelines for the Prophylaxis and Management of Tumor Lysis Syndrome (TLS). 1. Study Synopsis (Study Design) and Section 6.3 Dose-Limiting Toxicity: The text was edited to classify Grade >= 4 abnormalities in serum creatinine or electrolytes as DLTs; Grade >= 3 acute kidney injury defined as creatinine > 3 * baseline or > 4.0 mg/dL of any duration is to be considered a DLT; and occurrence of Grade >= 3 nausea, vomiting, constipation or diarrhea of > 7 days duration in spite of optimal management, including a 5-HT3 antagonist and aprepitant for nausea and vomiting, and loperamide (e.g., Imodium) and diphenoxylate/atropine (e.g. Lomotil) for diarrhea is to be considered a DLT. 2. Sections 6.5 and 6.6.1: Text was added to provide guidance for monitoring/prophylaxis and treatment of tumor lysis syndrome. Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Other significant changes. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document.

26 June 2014	The key changes in Amendment 3 are listed below: 1. Addition of the new Oprozomib ER formulation Tablets 2. Addition of the step-up dosing for dose escalation 3. Addition of additional clinic visits for safety assessments 4. Addition of PK and PD assessments based on new dosing and formulation 5. Addition of assessments of orthostatic hypotension and management 6. Updates to safety and efficacy information from oprozomib studies 7. Updates to Inclusion/Exclusion criteria 8. Updates to phototoxicity risk with oprozomib Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Changes in the schedules of assessments have been updated to be current with the revised study plan and assessment schedule.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31229804