Clinical trial results:
A Phase 2, Multi-Center, Randomized, Double-Blinded, Parallel Group Study of the Safety and Efficacy of Different Lenalidomide (REVLIMID®) Dose Regimens in Subjects With Relapsed or Refractory B-Cell Chronic Lymphocytic Leukemia

Summary

EudraCT number	2009-009836-54
Trial protocol	GB DE FR SE ES IT
Global end of trial date	04 September 2017

Results information

Result version number	v1 (current)
This version publication date	16 September 2018
First version publication date	16 September 2018

Trial information

Trial identification

Sponsor protocol code	CC-5013-CLL-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00963105
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, NJ, United States, 07901
Public contact	ClinicalTrialDisclosure, Celgene Corporation, +1 888-260-1599, ClinicalTrialDisclosure@celgene.com
Scientific contact	Jeffery Jones, Celgene Corporation, +1 (908) 673-9686, jejones@celgene.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	04 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL).

Protection of trial subjects:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	104
EEA total number of subjects	65

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)	52
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 29 sites from North America and Europe.

Pre-assignment

Screening details:

Participants were randomized (1:1:1) in a double-blind fashion, according to age (< 65 versus ≥ 65 years) and disease status (relapsed versus refractory) to their last purine-analog or bendamustine based prior regimen.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide 5 mg

Arm description:

Participants received a starting dose of 5 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	CC-5013
Other name	Revlimid®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered orally once a day in 28-day cycles.

Arm title	Lenalidomide 10 mg

Arm description:

Participants received a starting dose of 10 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	CC-5013
Other name	Revlimid®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered orally once a day in 28-day cycles.

Arm title	Lenalidomide 15 mg

Arm description:

Participants received a starting dose of 15 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable

toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	CC-5013
Other name	Revlimid®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered orally once a day in 28-day cycles.

Number of subjects in period 1	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg
Started	34	35	35
Received Treatment	34	34 [1]	35
Completed	34	35	35

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Completed indicate participants who discontinued the study.

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide 5 mg
Reporting group description:	
Participants received a starting dose of 5 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.	
Reporting group title	Lenalidomide 10 mg
Reporting group description:	
Participants received a starting dose of 10 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.	
Reporting group title	Lenalidomide 15 mg
Reporting group description:	
Participants received a starting dose of 15 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.	

Reporting group values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg
Number of subjects	34	35	35
Age categorical Units: Subjects			
< 65 years	16	19	17
≥ 65 years	18	16	18
Age continuous Units: years			
arithmetic mean	64.0	63.3	63.7
standard deviation	± 9.46	± 8.31	± 7.56
Gender categorical Units: Subjects			
Female	8	13	11
Male	26	22	24
Race Units: Subjects			
White	31	30	33
Black or African American	2	4	2
Other	0	1	0
Unknown	1	0	0

Reporting group values	Total		
Number of subjects	104		
Age categorical Units: Subjects			
< 65 years	52		
≥ 65 years	52		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	32		
Male	72		
Race Units: Subjects			
White	94		
Black or African American	8		
Other	1		
Unknown	1		

End points

End points reporting groups

Reporting group title	Lenalidomide 5 mg

Reporting group description:

Participants received a starting dose of 5 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Reporting group title	Lenalidomide 10 mg

Reporting group description:

Participants received a starting dose of 10 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Reporting group title	Lenalidomide 15 mg

Reporting group description:

Participants received a starting dose of 15 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Primary: Number of Participants With Treatment-emergent Adverse Events

End point title	Number of Participants With Treatment-emergent Adverse Events[1]

End point description:

Adverse events (AEs) were graded for severity by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 with the exceptions of hematologic toxicities and tumor lysis syndrome, according to the following scale: Grade 1 = Mild Grade 2 = Moderate Grade 3 = Severe Grade 4 = Life Threatening or disabling AE Grade 5 = Death The investigator determined the relationship of each AE to study drug based on the timing of the AE and whether other medications, therapeutic interventions, or underlying conditions could provide a sufficient explanation for the observed event.

End point type	Primary

End point timeframe:

From first dose of study drug to 30 days after the last dose; the maximum duration of treatment was 251, 265, and 267 weeks in the 5 mg, 10 mg, and 15 mg treatment groups respectively.

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 comparisons between treatment groups were not conducted in this study.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34[2]	34[3]	35[4]	
Units: participants				
Any adverse events	34	34	35	
Treatment-related adverse events (TRAE)	33	34	32	
Grade 3/4 adverse events	33	32	34	
Treatment-related Grade 3/4 adverse events	31	32	30	
Grade 5 adverse events	4	4	3	

Treatment-related Grade 5 adverse events	2	2	0	
Serious adverse events	24	24	27	
Treatment-related serious adverse events	15	13	20	
AEs leading to discontinuation of study drug	21	17	16	
TRAEs leading to discontinuation of study drug	16	14	13	
AEs leading to study drug dose reduction only	8	6	5	
AEs leading to study drug dose interruption only	25	24	25	
AEs leading to study drug interruption & reduction	18	26	19	

Notes:

[2] - Randomized participants who received at least one dose of study drug.

[3] - Randomized participants who received at least one dose of study drug.

[4] - Randomized participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall response rate was defined as the percentage of participants with a complete response (CR), CR with incomplete bone marrow recovery (CRi) or partial response (PR) during the treatment period. Tumor response was assessed by the investigator according to the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines for the diagnosis and treatment of CLL, based on laboratory, physical exam, assessment of constitutional symptoms and if appropriate computed tomography (CT) scan findings (to confirm PR or CR/CRi). For confirmed PR or CR/CRi, response had to be maintained for ≥ 8 weeks. Efficacy endpoints were analyzed in the intent-to-treat population which consisted of all randomized participants.

End point type	Secondary

End point timeframe:

Response was assessed after 3 cycles of therapy (Week 12) and every 4 weeks thereafter until disease progression. Maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	35	35	
Units: percentage of participants				
number (not applicable)	47.1	37.1	40.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Duration of Response

End point title	Kaplan-Meier Estimate of Duration of Response

End point description:

Duration of response (DOR) was defined as the time from the first visit where PR, CRi, or CR was documented to progressive disease (PD). Duration of response was censored at the last date that the participant was known to be progression-free for participants who had not progressed at the time of analysis or who withdrew consent or were lost to follow-up prior to documentation of progression. "99999" indicates data that could not be estimated due to the low number of events at the time of analysis.

End point type	Secondary

End point timeframe:

Response was assessed after 3 cycles of therapy (Week 12) and every 4 weeks thereafter until disease progression. Maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[5]	13[6]	14[7]	
Units: weeks				
median (confidence interval 95%)	101.1 (60.6 to 239.3)	35.1 (22.0 to 99999)	88.8 (72.1 to 127.3)	

Notes:

[5] - Randomized participants with an objective response (CR/CRi or PR)

[6] - Randomized participants with an objective response (CR/CRi or PR)

[7] - Randomized participants with an objective response (CR/CRi or PR)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response (TTR) was calculated as the time from randomization to the first documented date of response (PR, CRi or CR) based on iwCLL guidelines for participants with an objective response during the treatment period.

End point type	Secondary

End point timeframe:

Response was assessed after 3 cycles of therapy (Week 12) and every 4 weeks thereafter until disease progression. Maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[8]	13[9]	14[10]	
Units: weeks				
median (full range (min-max))	16.9 (12.1 to 74.1)	12.6 (8.4 to 52.1)	12.7 (12.0 to 147.3)	

Notes:

[8] - Randomized participants with an objective response (CR/CRi or PR)

[9] - Randomized participants with an objective response (CR/CRi or PR)

[10] - Randomized participants with an objective response (CR/CRi or PR)

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Time to Progression

End point title	Kaplan-Meier Estimate of Time to Progression

End point description:

Time to progression (TTP) was defined as the time from randomization to the first documented progression. For participants who did not progress during the study, TTP was censored at the last adequate response assessment showing evidence of no disease progression.

End point type	Secondary

End point timeframe:

From randomization until the end of the study; maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	35	35	
Units: weeks				
median (confidence interval 95%)	96.3 (20.6 to 251.3)	47.6 (31.9 to 261.1)	66.3 (20.1 to 89.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Event-Free Survival

End point title	Kaplan-Meier Estimate of Event-Free Survival

End point description:

Event-free survival (EFS) is the interval between the start of treatment to the first sign of disease progression, or treatment for relapse or death (whichever occurred first). If withdrawal of consent or loss to follow-up occurred before documented progression or death, then these observations were censored at the date when the last complete tumor assessments determined a lack of progression.

End point type	Secondary

End point timeframe:

From randomization until the end of the study; maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	35	35	
Units: weeks				
median (confidence interval 95%)	25.6 (16.1 to 77.6)	31.9 (21.1 to 47.6)	24.1 (13.4 to 66.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Progression Free Survival

End point title	Kaplan-Meier Estimate of Progression Free Survival

End point description:

Progression-free survival (PFS) was calculated as the time from randomization to the first documented progression or death due to any cause during or after the treatment period, whichever occurred first. The progression date was assigned to the earliest time when any progression is observed without prior missing assessments. If withdrawal of consent or loss to follow-up occurred before documented progression or death, then these observations were censored at the date when the last complete tumor assessments determined a lack of progression.

End point type	Secondary

End point timeframe:

From randomization until the end of the study; maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	35	35	
Units: weeks				
median (confidence interval 95%)	31.4 (16.1 to 96.3)	45.1 (22.4 to 120.1)	66.3 (16.1 to 89.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Overall Survival

End point title	Kaplan-Meier Estimate of Overall Survival

End point description:

Overall survival (OS) was defined as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who had withdrawn consent or were lost to follow-up before death was documented.

End point type	Secondary

End point timeframe:

From randomization until the end of the study; maximum time on study was 91 months.

End point values	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	35	35	
Units: weeks				
median (confidence interval 95%)	161.0 (64.9 to 209.0)	106.7 (83.4 to 235.7)	154.6 (80.9 to 214.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after the last dose; the maximum duration of treatment was 251, 265, and 267 weeks in the 5 mg, 10 mg, and 15 mg treatment groups respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Lenalidomide 5 mg

Reporting group description:

Participants received a starting dose of 5 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Reporting group title	Lenalidomide 10 mg

Reporting group description:

Participants received a starting dose of 10 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Reporting group title	Lenalidomide 15 mg

Reporting group description:

Participants received a starting dose of 15 mg lenalidomide orally once a day. Lenalidomide dose was escalated by 5 mg in a step-wise manner every 28 days up to a maximum dose of 25 mg daily based on tolerability. Participants continued receiving study drug until disease progression or unacceptable toxicity, unless they withdrew consent or had other reasons to discontinue from study drug.

Serious adverse events	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 34 (70.59%)	24 / 34 (70.59%)	27 / 35 (77.14%)
number of deaths (all causes)	24	23	26
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
ADENOCARCINOMA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ADENOCARCINOMA PANCREAS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
ANAL SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEN'S DISEASE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KERATOACANTHOMA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
LUNG ADENOCARCINOMA			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
MENINGIOMA BENIGN			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
METASTATIC SQUAMOUS CELL CARCINOMA			

subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
NEUROFIBROMA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
OLIGOASTROCYTOMA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR FLARE			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	6 / 35 (17.14%)
occurrences causally related to treatment / all	2 / 2	0 / 0	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS THROMBOSIS LIMB			

subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
DISEASE PROGRESSION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPAIRED HEALING			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
PAIN			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 2	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
DYSPNOEA			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOXIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
LUNG CONSOLIDATION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY OEDEMA			

subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ALCOHOL POISONING			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
FALL			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
Cardiac disorders			
ARRHYTHMIA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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

Nervous system disorders			
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
DIZZINESS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
SYNCOPE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
ANAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 34 (5.88%)	4 / 34 (11.76%)	4 / 35 (11.43%)
occurrences causally related to treatment / all	3 / 3	2 / 4	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMMUNE THROMBOCYTOPENIC PURPURA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LYMPHADENITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
NEUTROPENIA			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	1 / 1	1 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC INFARCTION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN			
subjects affected / exposed	0 / 34 (0.00%)	3 / 34 (8.82%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
DIARRHOEA			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			

subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
VOMITING			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
ACTINIC KERATOSIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EXFOLIATIVE RASH			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
SUBCUTANEOUS EMPHYSEMA			

subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
URTICARIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
RENAL FAILURE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
Musculoskeletal and connective tissue disorders			
ARTHRITIS REACTIVE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
BACK PAIN			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COCCYDYNIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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

GROIN PAIN			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
Infections and infestations			
ASPERGILLUS INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
ATYPICAL PNEUMONIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
BACTERAEMIA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPIDIDYMITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
EPIGLOTTITIS			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA SEPSIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS SALMONELLA			

subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
INFECTIOUS MONONUCLEOSIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
LUNG INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIC INFECTION			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL CANDIDIASIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 35 (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
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			

subjects affected / exposed	5 / 34 (14.71%)	4 / 34 (11.76%)	10 / 35 (28.57%)
occurrences causally related to treatment / all	2 / 6	1 / 4	4 / 12
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 1
PNEUMONIA INFLUENZAL			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
POST PROCEDURAL CELLULITIS			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALMONELLOSIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (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
SEPSIS			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOFT TISSUE INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			

subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYSTEMIC MYCOSIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBERCULOSIS OF PERIPHERAL LYMPH NODES			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
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	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	1 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERKALAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR LYSIS SYNDROME			

subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
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	Lenalidomide 5 mg	Lenalidomide 10 mg	Lenalidomide 15 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)	34 / 34 (100.00%)	35 / 35 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR FLARE			
subjects affected / exposed	17 / 34 (50.00%)	21 / 34 (61.76%)	23 / 35 (65.71%)
occurrences (all)	35	41	39
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	4 / 34 (11.76%)	4 / 34 (11.76%)	5 / 35 (14.29%)
occurrences (all)	4	4	10
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	2
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	4 / 34 (11.76%)	4 / 34 (11.76%)	4 / 35 (11.43%)
occurrences (all)	10	4	7
CHEST DISCOMFORT			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
CHILLS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	6 / 35 (17.14%)
occurrences (all)	0	4	6
FATIGUE			
subjects affected / exposed	18 / 34 (52.94%)	17 / 34 (50.00%)	23 / 35 (65.71%)
occurrences (all)	37	35	49
INFLUENZA LIKE ILLNESS			

subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	0 / 35 (0.00%)
occurrences (all)	3	4	0
LOCAL SWELLING			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
MALAISE			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences (all)	3	1	1
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
OEDEMA PERIPHERAL			
subjects affected / exposed	6 / 34 (17.65%)	8 / 34 (23.53%)	5 / 35 (14.29%)
occurrences (all)	8	9	7
PYREXIA			
subjects affected / exposed	12 / 34 (35.29%)	15 / 34 (44.12%)	16 / 35 (45.71%)
occurrences (all)	18	30	35
Immune system disorders			
HYPOGAMMAGLOBULINAEMIA			
subjects affected / exposed	5 / 34 (14.71%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	5	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	10 / 34 (29.41%)	15 / 34 (44.12%)	12 / 35 (34.29%)
occurrences (all)	11	27	25
DYSPHONIA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	3 / 35 (8.57%)
occurrences (all)	2	0	4
DYSPNOEA			
subjects affected / exposed	7 / 34 (20.59%)	6 / 34 (17.65%)	9 / 35 (25.71%)
occurrences (all)	8	13	18
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 34 (2.94%)	4 / 34 (11.76%)	3 / 35 (8.57%)
occurrences (all)	1	5	4
EPISTAXIS			

subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	3 / 35 (8.57%)
occurrences (all)	2	0	3
HYPOXIA			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	3 / 35 (8.57%)
occurrences (all)	2	1	4
NASAL CONGESTION			
subjects affected / exposed	4 / 34 (11.76%)	2 / 34 (5.88%)	3 / 35 (8.57%)
occurrences (all)	4	2	3
NASAL DRYNESS			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
OROPHARYNGEAL PAIN			
subjects affected / exposed	6 / 34 (17.65%)	1 / 34 (2.94%)	9 / 35 (25.71%)
occurrences (all)	9	2	9
PLEURAL EFFUSION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	0	3	2
PRODUCTIVE COUGH			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	5
RHINORRHOEA			
subjects affected / exposed	5 / 34 (14.71%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	5	0	0
SINUS CONGESTION			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	2	1	2
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	4 / 35 (11.43%)
occurrences (all)	0	2	4
DEPRESSION			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	2 / 35 (5.71%)
occurrences (all)	1	3	2
INSOMNIA			
subjects affected / exposed	3 / 34 (8.82%)	4 / 34 (11.76%)	8 / 35 (22.86%)
occurrences (all)	3	4	8

Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 34 (17.65%)	7 / 34 (20.59%)	5 / 35 (14.29%)
occurrences (all)	9	28	17
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 34 (8.82%)	4 / 34 (11.76%)	5 / 35 (14.29%)
occurrences (all)	5	24	10
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	2 / 34 (5.88%)	3 / 34 (8.82%)	1 / 35 (2.86%)
occurrences (all)	3	6	1
BLOOD CREATININE INCREASED			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	2	2	5
BLOOD IMMUNOGLOBULIN G DECREASED			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	5	7	0
WEIGHT DECREASED			
subjects affected / exposed	7 / 34 (20.59%)	13 / 34 (38.24%)	10 / 35 (28.57%)
occurrences (all)	18	22	16
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	3 / 34 (8.82%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	3	2	3
LACERATION			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
PROCEDURAL PAIN			

subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
TACHYCARDIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	6 / 34 (17.65%)	1 / 34 (2.94%)	4 / 35 (11.43%)
occurrences (all)	10	3	4
DYSGEUSIA			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	3 / 35 (8.57%)
occurrences (all)	4	0	8
HEADACHE			
subjects affected / exposed	5 / 34 (14.71%)	4 / 34 (11.76%)	4 / 35 (11.43%)
occurrences (all)	9	4	4
HYPOAESTHESIA			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	3	3	2
LETHARGY			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
NEUROPATHY PERIPHERAL			
subjects affected / exposed	3 / 34 (8.82%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	4	2	7
PARAESTHESIA			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	3 / 35 (8.57%)
occurrences (all)	2	4	3
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
SOMNOLENCE			

subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
TREMOR			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	2	6	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	11 / 34 (32.35%)	18 / 34 (52.94%)	15 / 35 (42.86%)
occurrences (all)	40	52	48
AUTOIMMUNE HAEMOLYTIC ANAEMIA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	6	0	0
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	2	2	2
LEUKOPENIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	6
LYMPH NODE PAIN			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	1	4	0
NEUTROPENIA			
subjects affected / exposed	25 / 34 (73.53%)	30 / 34 (88.24%)	26 / 35 (74.29%)
occurrences (all)	197	220	140
THROMBOCYTOPENIA			
subjects affected / exposed	17 / 34 (50.00%)	25 / 34 (73.53%)	21 / 35 (60.00%)
occurrences (all)	73	104	95
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Eye disorders			
DRY EYE			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
LACRIMATION INCREASED			

subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	1 / 35 (2.86%)
occurrences (all)	1	3	2
ABDOMINAL PAIN			
subjects affected / exposed	3 / 34 (8.82%)	10 / 34 (29.41%)	6 / 35 (17.14%)
occurrences (all)	5	18	8
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	3 / 35 (8.57%)
occurrences (all)	1	4	7
CONSTIPATION			
subjects affected / exposed	11 / 34 (32.35%)	13 / 34 (38.24%)	13 / 35 (37.14%)
occurrences (all)	11	15	22
DIARRHOEA			
subjects affected / exposed	14 / 34 (41.18%)	18 / 34 (52.94%)	16 / 35 (45.71%)
occurrences (all)	24	29	37
DRY MOUTH			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	6 / 35 (17.14%)
occurrences (all)	1	3	9
DYSPEPSIA			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	0 / 35 (0.00%)
occurrences (all)	1	3	0
DYSPHAGIA			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	5	0	1
GASTRITIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
NAUSEA			

subjects affected / exposed	10 / 34 (29.41%)	15 / 34 (44.12%)	11 / 35 (31.43%)
occurrences (all)	13	27	17
ORAL PAIN			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
STOMATITIS			
subjects affected / exposed	3 / 34 (8.82%)	1 / 34 (2.94%)	4 / 35 (11.43%)
occurrences (all)	7	1	10
VOMITING			
subjects affected / exposed	8 / 34 (23.53%)	5 / 34 (14.71%)	8 / 35 (22.86%)
occurrences (all)	8	6	12
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
HYPERBILIRUBINAEMIA			
subjects affected / exposed	4 / 34 (11.76%)	2 / 34 (5.88%)	3 / 35 (8.57%)
occurrences (all)	38	2	7
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	1 / 34 (2.94%)	5 / 34 (14.71%)	1 / 35 (2.86%)
occurrences (all)	1	6	1
EXFOLIATIVE RASH			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	0	3	6
HYPERHIDROSIS			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	7 / 35 (20.00%)
occurrences (all)	1	2	7
NIGHT SWEATS			
subjects affected / exposed	6 / 34 (17.65%)	10 / 34 (29.41%)	11 / 35 (31.43%)
occurrences (all)	10	13	16
PRURITUS			
subjects affected / exposed	3 / 34 (8.82%)	4 / 34 (11.76%)	3 / 35 (8.57%)
occurrences (all)	3	7	5
RASH			

subjects affected / exposed	9 / 34 (26.47%)	8 / 34 (23.53%)	16 / 35 (45.71%)
occurrences (all)	12	13	31
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	2	2	1
RASH GENERALISED			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	4	2	1
RASH MACULAR			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
RASH MACULO-PAPULAR			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	8
RASH PRURITIC			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
SKIN EXFOLIATION			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
SWELLING FACE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
URTICARIA PAPULAR			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	2 / 34 (5.88%)	4 / 34 (11.76%)	1 / 35 (2.86%)
occurrences (all)	2	6	2
HAEMATURIA			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
POLLAKIURIA			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	3	1	2

Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	6 / 34 (17.65%)	4 / 34 (11.76%)	2 / 35 (5.71%)
occurrences (all)	8	7	2
BACK PAIN			
subjects affected / exposed	4 / 34 (11.76%)	2 / 34 (5.88%)	10 / 35 (28.57%)
occurrences (all)	4	4	14
BONE PAIN			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	0	2	3
MUSCLE SPASMS			
subjects affected / exposed	6 / 34 (17.65%)	7 / 34 (20.59%)	11 / 35 (31.43%)
occurrences (all)	9	10	13
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	4 / 35 (11.43%)
occurrences (all)	2	2	5
NECK PAIN			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	3 / 35 (8.57%)
occurrences (all)	2	2	5
PAIN IN EXTREMITY			
subjects affected / exposed	8 / 34 (23.53%)	5 / 34 (14.71%)	5 / 35 (14.29%)
occurrences (all)	8	5	5
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	5 / 34 (14.71%)	2 / 34 (5.88%)	3 / 35 (8.57%)
occurrences (all)	8	5	5
CELLULITIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	0	4	2
CYTOMEGALOVIRUS INFECTION			

subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
HERPES SIMPLEX			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	4 / 35 (11.43%)
occurrences (all)	0	0	5
LABYRINTHITIS			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
LOCALISED INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
NASOPHARYNGITIS			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	7	0	2
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 34 (0.00%)	3 / 34 (8.82%)	3 / 35 (8.57%)
occurrences (all)	0	6	4
ORAL HERPES			
subjects affected / exposed	2 / 34 (5.88%)	3 / 34 (8.82%)	4 / 35 (11.43%)
occurrences (all)	2	3	5
OTITIS MEDIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
PHARYNGITIS			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	3 / 35 (8.57%)
occurrences (all)	1	1	4
PNEUMONIA			
subjects affected / exposed	2 / 34 (5.88%)	4 / 34 (11.76%)	5 / 35 (14.29%)
occurrences (all)	2	5	5
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0

RHINITIS			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	2 / 35 (5.71%)
occurrences (all)	1	9	5
SALMONELLOSIS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
SINUSITIS			
subjects affected / exposed	4 / 34 (11.76%)	1 / 34 (2.94%)	3 / 35 (8.57%)
occurrences (all)	6	2	4
SKIN INFECTION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	4
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	1 / 35 (2.86%)
occurrences (all)	0	3	1
TOOTH INFECTION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 34 (23.53%)	5 / 34 (14.71%)	3 / 35 (8.57%)
occurrences (all)	10	13	7
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 34 (11.76%)	5 / 34 (14.71%)	2 / 35 (5.71%)
occurrences (all)	10	8	2
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	7 / 35 (20.00%)
occurrences (all)	4	1	16
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	5 / 34 (14.71%)	11 / 34 (32.35%)	9 / 35 (25.71%)
occurrences (all)	5	21	12
DEHYDRATION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
HYPERCALCAEMIA			

subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	6	2	2
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	5	2	2
HYPERKALAEMIA			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences (all)	6	1	1
HYPOCALCAEMIA			
subjects affected / exposed	3 / 34 (8.82%)	2 / 34 (5.88%)	2 / 35 (5.71%)
occurrences (all)	10	2	2
HYPOKALAEMIA			
subjects affected / exposed	5 / 34 (14.71%)	5 / 34 (14.71%)	5 / 35 (14.29%)
occurrences (all)	6	9	7
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 34 (2.94%)	4 / 34 (11.76%)	1 / 35 (2.86%)
occurrences (all)	1	5	1
HYPONATRAEMIA			
subjects affected / exposed	1 / 34 (2.94%)	1 / 34 (2.94%)	2 / 35 (5.71%)
occurrences (all)	1	1	3
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	2 / 35 (5.71%)
occurrences (all)	2	3	3
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2009	Amendment 1 included the following changes: - Added back-up North American and 24-hour European emergency medical contacts. - Clarified which assessments could be performed for subjects who discontinued the study but continued to be assessed for response until disease progression. - Updated to allow greater investigator discretion in determining thromboembolic prophylaxis regimen based on individual subject status. - Corrections to the Schedule of Assessments: - Clarified that 28-day visit could be the 1st day of each new cycle, and to reflect that 84 days equaled to 12 weeks (not 16 weeks). - The "for Central Pathology Reviewer" was deleted from the procedure name ("Bone marrow aspirate, biopsy, peripheral blood slides") to avoid confusion. In addition to submission of samples for central pathology review, local pathology review of the bone marrow aspirate and biopsy samples was also required. - Although specified in the respective footnote, "CR/CRi only" was added to clarify that the assessments MRD evaluation and bone marrow biopsy slides and/or aspirate for biomarker analyses, were only required for a CR/CRi confirmation visit, not a PR confirmation visit. - Corrected interval for follow-up ECG assessment to reflect 84 days equals 12 weeks (not 16 weeks). - Added details to clarify required central versus local clinical laboratory assessments (hematology, chemistry, and urinalysis). - Corrected interval for follow-up TSH assessment to reflect 84 days equals 12 weeks (not 16 weeks). - Updated footnote to specify time points for exploratory assessments and that those were to be analyzed centrally. - Updated to specify a maximum number of lymph node biopsies that could be performed for any one subject enrolled into the lymph node biopsy substudy. - Added statement to clarify that PK and exploratory biomarker assessments were to be analyzed centrally. - Added the average dose of radiation exposure per CT scan as required by IECs/IBs.
11 February 2010	Amendment 2 included the following key changes: - For select exploratory assessments: - Sampling time points for select exploratory assessments were revised to better support the exploratory objectives of the study. These assessments included the cytokines/soluble protein analysis, immune and B-CLL cells analysis by flow cytometry and immune cell and B-CLL cell activation, protein expression, and functional studies and micro-ribonucleic acid (miRNA) and gene expression profiling. - Tumor Protein 53 mutation analysis was added to the protocol based on recent publications and presentation at major international hematology meetings; it was to be performed at screening on the same sample as those collected for the VH mutational status analysis and was not to require additional blood sampling. - Added to the protocol that for subjects enrolled in Europe, SNP/mutational status analysis could also be performed from CD19 isolated cells if sufficient sample was available from the ZAP-70, VH mutational status/TP53 mutation analysis, and FISH studies. The sampling for gene copy number/SNP analysis that was part of the optional testing was deleted from the study. - Added to the protocol that for subjects enrolled in the US/Canada, an additional exploratory MRD marker analysis could be performed on the same sample as that collected for disease diagnosis confirmation and MRD evaluation. - The maximum number of prior treatment regimen for B-CLL was increased from 3 to 4. - Additional guidance was added to emphasize the importance of monitoring subjects' platelet counts during the study. - The 24-hour emergency call center information was added to the protocol as this was implemented for all Celgene-sponsored studies to ensure subject safety. - Added further details on when study drug had to be permanently discontinued in case of renal insufficiency. - Added details on AE reporting timeframes required for the study.

09 December 2010	Amendment 3 included the following changes: - Based on delayed enrollment, the number of planned subjects was decreased from up to 120 to up to 90. - The frequency of visits during Cycles 2, 3 and 4 were decreased. - Changes to eligibility criteria: - Removed cap on the number of prior treatment regimens for B-CLL. - Allowed inclusion of subjects with prior treatment with either a purine-analog or bendamustine based regimen. - Stratification factor was updated to include relapsed versus refractory to a purine-analog or bendamustine based regimen (if subject had received both, status post most recent regimen was to be used). - The 120-day washout period for prior alemtuzumab treatment was decreased to 60 days. - Inclusion criteria were changed to allow screening of subjects with prior history of carcinoma in situ of the bladder if the subject was disease free for < 2 years prior to enrollment. - Since this was a Phase 2 study, the following administrative decisions were made: - Study was to be closed once 80% of randomized subjects had progressed or died. All subjects on study drug at the time the study was closed were to be transferred to commercial drug on a free basis. Survival follow-up was to cease at study closure. - CT scans for lymph nodes, liver, and spleen were not to be reviewed centrally. - To simplify laboratory sampling, the following exploratory assessments were removed: - Immune and B-CLL cells analysis by flow cytometry, cell activation, protein expression, and functional studies - Micro-ribonucleic acid and gene expression profiling - Bone marrow biopsy slides and/or aspirate for biomarker analyses - Sampling for prognostic factors and confirmation of disease diagnosis were to be performed at baseline instead of screening. - An exploratory substudy involving FNA of lymph nodes was added. - sampling time points for the cytokine and soluble protein biomarker assay and sparse PK were updated.
11 May 2011	Amendment 4 included the following key changes: - Required that SPMs were collected and monitored as SAEs and reported throughout the study duration, from the time of signing the informed consent up to and including the survival follow up phase. Subjects were followed until 80% of the subjects had progressed or died or up to 5 years after the last subject was randomized, whichever came later. - Incorporated current Celgene Pregnancy Prevention Plan language regarding the risks of lenalidomide and other text regarding source data verification.
09 November 2011	Amendment 5 included the following key changes: - Increased the sample size and required that following the enrollment of 90 subjects, participation in the PK substudy was mandatory. - Clarified that the second primary malignancy assessment had to be completed during the PFS follow-up phase and the survival phase. - Clarified the schedule for the baseline bone marrow biopsy and aspirate, which could be completed either during the screening phase or could be completed once the subject had been confirmed as eligible and entered into the study. - Expanded exclusion criteria surrounding history of prior malignancies from 2 years to 5 years. - Updated study contact information (clinical research physician and study manager).

14 April 2015	Amendment 6 included the following key changes: - The study drug packaging was changed from blister cards to bottles. - Subjects on study drug at the time of study closure could transition to non-study lenalidomide. - IVRS was discontinued. Sites ordered study drug when needed through the Celgene investigational drug dispensing program. This permitted sites to order study drug only when needed rather than maintain a stock of study drug for the IVRS to allocate. The change was possible at that time since few subjects remained on study drug and the study drug was no longer blinded. - Removed the 1.25-mg dose level and applied corresponding changes in the Dose Reduction Steps for Lenalidomide as no subjects utilized this dose level. - As all subjects were beyond the risk for TLS, Celgene no longer provided allopurinol supply for sites outside of North America. - Removed lymph node biopsy and fine needle aspirate assessments as no subjects consented for these additional tests. - Removed additional PK sample collection. PK samples were drawn at Study Day 1 and at dose escalation. Since the last subject was randomized in 2012, further dose escalations were not anticipated and hence no further PK samples were collected. - Removed the requirement to submit blood samples (hematology, chemistry, thyroid hormone, quantitative immunoglobulins and MRD), urine (urinalysis) and bone marrow (biopsy and aspirate) samples to the central laboratory for analysis. Local laboratories continued to be collected. The purpose of this change was to simplify the protocol procedures to reduce the workload for site personnel. - Removed the blood drawn for cytokines at the start and end of tumor flare. Tumor flare events were anticipated at the start of study drug administration. Since the last subject was randomized in 2012, additional events of tumor flare were not anticipated. - Removed the text for blinding and emergency unblinding activities as the study was unblinded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported