Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Lenalidomide (Revlimid®) as Maintenance Therapy for Patients with B-Cell Chronic Lymphocytic Leukemia Following Second-Line Therapy (The Continuum Trial)

Summary

EudraCT number	2007-001626-27
Trial protocol	GB DE BE ES HU CZ PT AT IT DK FR SE NL IE BG
Global end of trial date	27 October 2020

Results information

Result version number	v2 (current)
This version publication date	13 May 2023
First version publication date	12 November 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CC-5013-CLL-002

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the efficacy of lenalidomide versus placebo maintenance therapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Czechia: 18
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 21

Worldwide total number of subjects	317
EEA total number of subjects	142

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)	185
From 65 to 84 years	132
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

317 randomized and 315 treated

Period 1

Period 1 title	Pre-treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study was unblinded in 2016 after reaching the required number of progression events.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide

Arm description:

2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR

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

Dosage and administration details:

2.5mg - 10mg QD PO (x 28-day cycle)

Arm title	Placebo

Arm description:

2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR

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

Dosage and administration details:

QD PO (x 28-day cycle)

Number of subjects in period 1	Lenalidomide	Placebo
Started	160	157
Completed	158	157
Not completed	2	0
Other reasons	2	-

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study was unblinded in 2016 after reaching the required number of progression events.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide

Arm description:

2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR

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

Dosage and administration details:

2.5mg - 10mg QD PO (x 28-day cycle)

Arm title	Placebo

Arm description:

2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR

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

Dosage and administration details:

QD PO (x 28-day cycle)

Number of subjects in period 2	Lenalidomide	Placebo
Started	158	157
Subjects Escalated to 5mg	129	149
Subjects Escalated to 10mg	68	88
Completed	0	0
Not completed	158	157
PD with histologic transformation	4	2
Adverse event, serious fatal	4	-
Consent withdrawn by subject	5	2
PD without histologic transformation	51	111
Adverse event, non-fatal	61	15
Other reasons	32	26
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide
Reporting group description:	
2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR	
Reporting group title	Placebo
Reporting group description:	
2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR	

Reporting group values	Lenalidomide	Placebo	Total
Number of subjects	160	157	317
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	92	93	185
From 65-84 years	68	64	132
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	62.9	62.5	
standard deviation	± 8.08	± 8.85	-
Sex: Female, Male Units: Participants			
Female	45	44	89
Male	115	113	228
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	2	5
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	1	4	5
White	154	150	304
More than one race	0	0	0
Unknown or Not Reported	2	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	1	7
Not Hispanic or Latino	153	156	309

Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Lenalidomide
Reporting group description:	
2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR	
Reporting group title	Placebo
Reporting group description:	
2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR	
Reporting group title	Lenalidomide
Reporting group description:	
2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR	
Reporting group title	Placebo
Reporting group description:	
2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) is defined as the time from randomization to death from any cause. OS will be 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 were lost to follow-up before death was documented.	
End point type	Primary
End point timeframe:	
Up to 12 years	

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	157		
Units: Months				
median (confidence interval 95%)	95.09 (70.35 to 103.52)	73.28 (59.98 to 102.98)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Lenalidomide v Placebo

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.15

Notes:

[1] - The p-value is based on a stratified log-rank test.

Secondary: Progression Free Survival 2 (PFS2)

End point title	Progression Free Survival 2 (PFS2)

End point description:

Progression Free Survival (PFS2) assessed by investigator is defined as the time from randomization to the second objective disease progression, or death from any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Up to 6 years

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	154		
Units: Months				
median (confidence interval 95%)	99999 (49.5 to 99999)	35.9 (27.4 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Participants with Adverse Events (AEs)

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

End point description:

Incidence of participants with adverse events (AEs) that measure type, frequency and severity of AEs graded by National Cancer Institute Common Terminology Criteria (NCI CTCAE V 3.0) including any grade adverse events (AEs), Grade 3-4 AEs, AEs related to study drug, grade 3-4 AEs related to study drug.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to 9 years)

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	157		
Units: Participants				
Adverse Events (AEs)	155	149		
Grade 3-4 AEs	136	73		
AEs related to Study drugs	143	98		
Grade 3-4 AEs related to Study drugs	117	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 9 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR

Reporting group title	Lenalidomide

Reporting group description:

2.5mg QD PO with escalation after 28 days to 5mg QD PO x 28 days, only if the 2.5mg dose was tolerated. Participants could be escalated to 10mg QD PO x 28 days, but only after 5 continuous cycles at 5mg and only if 5mg was well tolerated and if those participants had not achieved MRD-negative CR

Serious adverse events	Placebo	Lenalidomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 157 (31.21%)	99 / 158 (62.66%)	
number of deaths (all causes)	80	78	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	8 / 157 (5.10%)	9 / 158 (5.70%)	
occurrences causally related to treatment / all	5 / 15	6 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage III			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 157 (1.27%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine carcinoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	4 / 157 (2.55%)	8 / 158 (5.06%)	
occurrences causally related to treatment / all	3 / 8	3 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour flare			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue inflammation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 157 (1.91%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 157 (0.64%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 157 (0.64%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 157 (0.64%)	4 / 158 (2.53%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	2 / 157 (1.27%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 157 (1.27%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelination			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplegia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia haemolytic autoimmune			
subjects affected / exposed	2 / 157 (1.27%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune pancytopenia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	0 / 157 (0.00%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 157 (0.64%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 157 (0.00%)	7 / 158 (4.43%)	
occurrences causally related to treatment / all	0 / 0	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	13 / 157 (8.28%)	49 / 158 (31.01%)	
occurrences causally related to treatment / all	16 / 18	71 / 76	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye movement disorder			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuropathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 157 (0.64%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			

subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis herpetiformis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 157 (1.27%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone tuberculosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr viraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 157 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 157 (0.64%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster ophthalmic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 157 (5.10%)	7 / 158 (4.43%)	
occurrences causally related to treatment / all	2 / 11	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia primary atypical			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 157 (0.00%)	5 / 158 (3.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Salmonella sepsis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis bacterial			

subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pericarditis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral labyrinthitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 157 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Lenalidomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 157 (89.17%)	152 / 158 (96.20%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare			
subjects affected / exposed	9 / 157 (5.73%)	12 / 158 (7.59%)	
occurrences (all)	14	18	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 157 (7.64%)	8 / 158 (5.06%)	
occurrences (all)	15	10	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 157 (0.64%)	10 / 158 (6.33%)	
occurrences (all)	1	11	
Asthenia			
subjects affected / exposed	2 / 157 (1.27%)	10 / 158 (6.33%)	
occurrences (all)	2	10	
Influenza like illness			
subjects affected / exposed	2 / 157 (1.27%)	11 / 158 (6.96%)	
occurrences (all)	2	18	
Oedema peripheral			
subjects affected / exposed	12 / 157 (7.64%)	16 / 158 (10.13%)	
occurrences (all)	22	20	
Fatigue			
subjects affected / exposed	54 / 157 (34.39%)	56 / 158 (35.44%)	
occurrences (all)	88	121	
Pyrexia			

subjects affected / exposed	17 / 157 (10.83%)	28 / 158 (17.72%)	
occurrences (all)	26	45	
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	10 / 157 (6.37%)	4 / 158 (2.53%)	
occurrences (all)	10	6	
Oropharyngeal pain			
subjects affected / exposed	16 / 157 (10.19%)	15 / 158 (9.49%)	
occurrences (all)	19	21	
Dyspnoea			
subjects affected / exposed	11 / 157 (7.01%)	16 / 158 (10.13%)	
occurrences (all)	15	19	
Cough			
subjects affected / exposed	32 / 157 (20.38%)	46 / 158 (29.11%)	
occurrences (all)	44	102	
Rhinorrhoea			
subjects affected / exposed	4 / 157 (2.55%)	10 / 158 (6.33%)	
occurrences (all)	6	11	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 157 (6.37%)	10 / 158 (6.33%)	
occurrences (all)	13	11	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	4 / 157 (2.55%)	8 / 158 (5.06%)	
occurrences (all)	9	8	
Weight increased			
subjects affected / exposed	9 / 157 (5.73%)	5 / 158 (3.16%)	
occurrences (all)	10	7	
Weight decreased			
subjects affected / exposed	14 / 157 (8.92%)	22 / 158 (13.92%)	
occurrences (all)	18	42	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 157 (5.73%)	16 / 158 (10.13%)	
occurrences (all)	12	21	

Headache			
subjects affected / exposed	14 / 157 (8.92%)	17 / 158 (10.76%)	
occurrences (all)	38	20	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	44 / 157 (28.03%)	106 / 158 (67.09%)	
occurrences (all)	80	479	
Leukopenia			
subjects affected / exposed	2 / 157 (1.27%)	12 / 158 (7.59%)	
occurrences (all)	2	21	
Anaemia			
subjects affected / exposed	7 / 157 (4.46%)	9 / 158 (5.70%)	
occurrences (all)	17	13	
Thrombocytopenia			
subjects affected / exposed	19 / 157 (12.10%)	44 / 158 (27.85%)	
occurrences (all)	29	103	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 157 (5.73%)	18 / 158 (11.39%)	
occurrences (all)	12	21	
Diarrhoea			
subjects affected / exposed	26 / 157 (16.56%)	65 / 158 (41.14%)	
occurrences (all)	45	165	
Dyspepsia			
subjects affected / exposed	8 / 157 (5.10%)	12 / 158 (7.59%)	
occurrences (all)	10	12	
Constipation			
subjects affected / exposed	8 / 157 (5.10%)	27 / 158 (17.09%)	
occurrences (all)	14	42	
Abdominal pain upper			
subjects affected / exposed	4 / 157 (2.55%)	9 / 158 (5.70%)	
occurrences (all)	9	12	
Nausea			
subjects affected / exposed	27 / 157 (17.20%)	26 / 158 (16.46%)	
occurrences (all)	39	36	
Vomiting			

subjects affected / exposed	13 / 157 (8.28%)	12 / 158 (7.59%)	
occurrences (all)	22	15	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 157 (1.27%)	8 / 158 (5.06%)	
occurrences (all)	4	9	
Hyperhidrosis			
subjects affected / exposed	5 / 157 (3.18%)	11 / 158 (6.96%)	
occurrences (all)	5	11	
Pruritus			
subjects affected / exposed	9 / 157 (5.73%)	20 / 158 (12.66%)	
occurrences (all)	10	32	
Rash			
subjects affected / exposed	13 / 157 (8.28%)	42 / 158 (26.58%)	
occurrences (all)	20	71	
Night sweats			
subjects affected / exposed	31 / 157 (19.75%)	30 / 158 (18.99%)	
occurrences (all)	58	50	
Actinic keratosis			
subjects affected / exposed	3 / 157 (1.91%)	10 / 158 (6.33%)	
occurrences (all)	6	20	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	20 / 157 (12.74%)	18 / 158 (11.39%)	
occurrences (all)	43	21	
Arthralgia			
subjects affected / exposed	10 / 157 (6.37%)	23 / 158 (14.56%)	
occurrences (all)	19	35	
Musculoskeletal pain			
subjects affected / exposed	7 / 157 (4.46%)	11 / 158 (6.96%)	
occurrences (all)	10	19	
Muscle spasms			
subjects affected / exposed	10 / 157 (6.37%)	22 / 158 (13.92%)	
occurrences (all)	18	34	
Myalgia			

subjects affected / exposed	8 / 157 (5.10%)	4 / 158 (2.53%)	
occurrences (all)	8	4	
Pain in extremity			
subjects affected / exposed	6 / 157 (3.82%)	13 / 158 (8.23%)	
occurrences (all)	18	15	
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 157 (7.64%)	22 / 158 (13.92%)	
occurrences (all)	21	33	
Herpes zoster			
subjects affected / exposed	9 / 157 (5.73%)	9 / 158 (5.70%)	
occurrences (all)	12	10	
Lower respiratory tract infection			
subjects affected / exposed	7 / 157 (4.46%)	12 / 158 (7.59%)	
occurrences (all)	9	16	
Influenza			
subjects affected / exposed	3 / 157 (1.91%)	14 / 158 (8.86%)	
occurrences (all)	4	17	
Nasopharyngitis			
subjects affected / exposed	18 / 157 (11.46%)	16 / 158 (10.13%)	
occurrences (all)	29	34	
Respiratory tract infection			
subjects affected / exposed	10 / 157 (6.37%)	14 / 158 (8.86%)	
occurrences (all)	19	20	
Oral herpes			
subjects affected / exposed	7 / 157 (4.46%)	10 / 158 (6.33%)	
occurrences (all)	8	13	
Pharyngitis			
subjects affected / exposed	7 / 157 (4.46%)	10 / 158 (6.33%)	
occurrences (all)	8	11	
Sinusitis			
subjects affected / exposed	5 / 157 (3.18%)	16 / 158 (10.13%)	
occurrences (all)	8	23	
Pneumonia			
subjects affected / exposed	2 / 157 (1.27%)	10 / 158 (6.33%)	
occurrences (all)	2	15	

Upper respiratory tract infection			
subjects affected / exposed	28 / 157 (17.83%)	31 / 158 (19.62%)	
occurrences (all)	68	53	
Viral infection			
subjects affected / exposed	5 / 157 (3.18%)	8 / 158 (5.06%)	
occurrences (all)	6	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 157 (5.73%)	15 / 158 (9.49%)	
occurrences (all)	10	19	
Hypokalaemia			
subjects affected / exposed	3 / 157 (1.91%)	10 / 158 (6.33%)	
occurrences (all)	3	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2008	Inclusion and Exclusion Criteria Update
24 April 2015	Study Endpoints Update
13 May 2016	Study Design Update
16 March 2018	Study Design Update

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported