



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 high-risk patients with chronic lymphocytic leukemia following first-line therapy

Summary

EudraCT number	2011-004698-98
Trial protocol	DE AT IT ES NL
Global end of trial date	14 January 2021

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	CLLM1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01556776
WHO universal trial number (UTN)	-
Other trial identifiers	Celgene Protocol Number: RV-CLL-GCLLSG-0725

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	CLLM1-Help Desk, Deutsche CLL-Studiengruppe, 49 22147888220, cllstudie@uk-koeln.de
Scientific contact	CLLM1-Help Desk, Deutsche CLL-Studiengruppe, 49 22147888220, cllstudie@uk-koeln.de

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	14 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2021
Global end of trial reached?	Yes
Global end of trial date	14 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:

- To compare the efficacy of lenalidomide versus placebo maintenance therapy. The primary efficacy objective of this study is to investigate if lenalidomide maintenance therapy is superior to placebo maintenance therapy in prolonging progression free survival (PFS), for subjects with a high risk of early progression following first-line treatment. All subjects, including both subjects who do and do not achieve MRD negativity will be treated up to disease progression with maintenance therapy.

Secondary Objective:

- To evaluate the prolongation of overall survival (OS) of lenalidomide versus placebo maintenance therapy
- To evaluate the safety of lenalidomide versus placebo maintenance therapy.

Protection of trial subjects:

Prophylaxis for TLS, thromboembolism and infection and treatment of tumor flare reaction (TFR)
In subjects with bulky disease (at least one lymph node >5cm in the largest diameter) TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated 3 days prior to starting maintenance therapy and for a minimum of the first treatment cycle at each dose level. Subjects with bulky disease and a known allergy to allopurinol will be excluded from the study. Subjects should be closely monitored for evidence of arterial and venous thromboembolic events while on study drug. Modifiable risk factors for thromboembolic events should be managed wherever possible (eg, smoking cessation; control of hypertension and hyperlipidaemia). Medicines that may increase the risk of thromboembolism, such as oestrogens and erythropoietic agents, should be used with caution during lenalidomide treatment. In case of hospitalization the subject should receive appropriate antithrombotic medication during the duration of the hospitalization. The investigator may use appropriate anti coagulation prophylactic therapies (i.e. LMW heparin, fondaparinux, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (i.e. subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history). In case of contraindications for prophylactic anti coagulation medication, compression stockings are recommended. Subjects with no history of DVT or arterial thromboembolic events within the past 12 months, no clear indication or contraindication for antiplatelet or anticoagulant therapy, with no active bleeding, and who are not considered to be at high risk of bleeding should receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug

Background therapy:

Published analyses revealed that subjects with a median progression free survival (PFS) of < 24 months after randomization showed a significantly shorter overall survival (OS) compared with subjects achieving a PFS of ≥ 24 months. 15 % of these subjects were characterized by both, the presence of 17p deletions and TP53 gene mutations, another 7.5% by TP53 mutation alone. Interestingly, the majority of subjects with a poor prognosis could not be defined by a mutation of TP53 or del(17p). An analysis showed that a combination of minimal residual disease (MRD) levels of $\geq 10^{-2}$ or a combination of MRD levels of $\geq 10^{-4}$ to $< 10^{-2}$ plus at least one of the three parameters (del(17p) or TP53 mutation or an unmutated IGHV-status) defined a group of subjects at high risk of early progression (HR). The median PFS of HR subjects was 22 months, the median PFS for subjects defined as low risk (LR; n=103) was 69 months. HR subjects had a 6.4 fold increased risk for progression (HR 6.4, 95% CI: 3.970-10.347; $p < 0.0001$) and a 5.7 fold increased risk for death, with a median OS of only 57 months (assessed from the beginning of FCR therapy). In contrast, median OS was not reached in the LR group at the time point of the analyses (HR 5.758, 95% CI: 2.799-11.844, $p < 0.0001$). The combined use of genetic markers and an MRD assessment two months after the completion of first line treatment (final

restaging) allows the identification of CLL subjects with a very poor prognosis after FCR therapy. The high risk group identified by this approach should be treated within clinical trials using novel strategies including maintenance protocols.

Evidence for comparator:

Although maintenance therapy has been established in recent years for the treatment of a subset of subjects with Non-Hodgkin's Lymphoma (NHL), it is a novel concept in the management of CLL. It is not regularly used and only a limited number of small studies have been conducted evaluating consolidation/maintenance therapy for limited periods of time with alemtuzumab or rituximab. Based on the limited amount of available data, it appears that maintenance therapy may improve the quality of remission in CLL subjects and prolong progression-free survival (PFS). A large phase 3 trial investigating lenalidomide as maintenance following response to second line therapy is ongoing. However, a large well-controlled study had not been conducted to investigate the beneficial effect of maintenance therapy following front line therapy; specifically in subjects with aggressive disease. This phase 3 study will evaluate whether lenalidomide maintenance therapy will prolong PFS in CLL subjects with a high risk of early progression following first line treatment.

Actual start date of recruitment	01 May 2012
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	Netherlands: 5
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	89
EEA total number of subjects	89

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)	48
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially planned sample size: 200 (186 plus 7.5% drop out rate) subjects should be enrolled and randomized (2:1) to lenalidomide daily or placebo daily until disease progression. Randomization has been closed early in March 2016 because of slow recruitment. 468 patients were screened for eligibility and a total of 89 patients had been randomized.

Pre-assignment

Screening details:

Patients who had responded to first-line chemoimmunotherapy, and a high risk for early progression defined as a MRD level in the peripheral blood of $\geq 10^{-2}$ (1 in 100 cells) or a combination of MRD levels of $\geq 10^{-4}$ to less than 10^{-2} plus at least one of three genetic characteristics (del[17p] or TP53 mutation or an unmutated IGHV-status) were eligible

Pre-assignment period milestones

Number of subjects started	468 ^[1]
Number of subjects completed	89

Pre-assignment subject non-completion reasons

Reason: Number of subjects	progressive disease during screening: 11
Reason: Number of subjects	low risk: 347
Reason: Number of subjects	Consent withdrawn by subject: 15
Reason: Number of subjects	4 administrative, 2 lost: 6

Notes:

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

Justification: 468 patients were screened for eligibility and a total of 89 patients had been randomized for the study.

Period 1

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

Blinding implementation details:

An electronic web/voicemail randomisation system (IWRS) with a secure, passwordprotected database on the basis of a computer-generated randomization schedule prepared by ICON (Dublin,Ireland) was used. Neither the sponsor nor the investigators had access to the randomisation schedule. Investigators, patients, study sponsor, and sponsor were all masked to the actual treatment; capsules that were identical in appearance were provided.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide daily starting with 5 mg daily on days 1-28 of the first 28-day cycle. If the 5 mg dose level is well tolerated, escalation to 10 mg daily on days 1-28 of each 28-day cycle is permitted starting with the second and up to the sixth cycle; further escalations starting with the 7th cycle and up to the 12th cycle to 15 mg daily is permitted. If after 12 cycles of treatment subjects still present with MRD levels of $\geq 10^{-4}$ in peripheral blood and previous dose levels are well tolerated, starting with the 13th cycle up to progression 20 mg daily is permitted. If after 18 cycles of treatment for subjects still present with MRD levels of $\geq 10^{-4}$ in peripheral blood and previous dose levels are well tolerated, starting with the 19th cycle up to progression 25 mg daily is permitted. 25 mg is the maximal daily dose of lenalidomide.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Equivalent to the lenalidomid arm

Number of subjects in period 1	Lenalidomide	Placebo
Started	60	29
Completed	21	14
Not completed	39	15
Consent withdrawn by subject	3	4
death	16	4
Other	14	5
missing information	2	2
did not receive any study treatment	4	-

Baseline characteristics

Reporting groups

Reporting group title	Lenalidomide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Lenalidomide	Placebo	Total
Number of subjects	60	29	89
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)	33	15	48
From 65-84 years	27	14	41
85 years and over	0	0	0
Age continuous Units: years			
median	64	64	
inter-quartile range (Q1-Q3)	57.3 to 69.8	58.0 to 69.5	-
Gender categorical Units: Subjects			
Female	7	6	13
Male	53	23	76
Cytogenetic abnormalities IGHV status			
Somatic mutations in IGHV genes are known prognostic marker in CLL: Mutated IGHV correlates with marked improvement in both progression free survival (PFS) and overall survival (OS), while patients with IGHV unmutated CLL have inferior duration of response to chemoimmunotherapy.			
Units: Subjects			
IGHV mutated	5	2	7
IGHV unmutated	50	24	74
missing	5	3	8
Cytogenetic abnormalities Deletion 17p			
Del 17p/TP53 alterations are the most important prognostic and predictive markers in CLL, they have been shown to convey resistance to standard chemo(immuno)therapies, such as fludarabine, cyclophosphamide and rituximab.			
Units: Subjects			
del(17p) present	7	2	9
del(17p) absent	45	24	69
missing	8	3	11
Cytogenetic abnormalities TP53 mutation Units: Subjects			
TP53 mutated	10	7	17

TP53 unmutated	46	20	66
Missing	4	2	6
CLL-IPI Risk Group			
To reduce the overwhelming prognostic information to a few clinically relevant, essential prognostic parameters, comprehensive prognostic scores have been constructed that combine clinical, biological and genetic information. The currently most relevant prognostic score is the CLL International Prognostic Index (CLL-IPI). It uses a weighted grading of five independent prognostic factors: TP53 deletion and/or mutation (collectively called TP53 dysfunction), IGHV mutational status, serum β 2-microglobulin, clinical stage, and age. The CLL-IPI separates four groups with different OS at 5years.			
Units: Subjects			
Low	2	0	2
Intermediate	5	2	7
High	16	11	27
Very HIgh	8	2	10
Missing	29	14	43
Cumulative Illness Rating Scale (CIRS)			
The CIRS rating scale is used to assess comorbidity, and is widely used in patients with CLL. CLL induced illness or organ damage are not included in this rating scale. If there are two or more illness/impairments of one organ system, the illness/impairment with the highest severity should be evaluated.			
Units: Score			
median	2	2	
inter-quartile range (Q1-Q3)	0 to 4	0.5 to 4	-

End points

End points reporting groups

Reporting group title	Lenalidomide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Progression-free survival according to independent review committee

End point title	Progression-free survival according to independent review committee
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End point description:

Because the median progression-free survival in the Lenalidomide study treatment arm was not reached and the upper range of the 95% confidence interval was not estimable (95%CI 32.3 months - not estimable), the progression rates (percentages, rounded to the nearest whole number) at 12 and 24 months are given. The median progression-free survival in the Placebo study treatment arm was 13.3 months (95%CI: 9.9-19.7). $P = 0.000001$ (by log-rank test stratified by MRD Status at randomization).

End point type	Primary
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End point timeframe:

PFS according to independent Review Committee was analysed within the interim analysis (data cut-off was 31.03.2016) . Median observation time at time point of this analysis was 17.9 months. This analysis was not repeated for the final analysis.

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	29		
Units: percentage				
12 months-survival	90	57		
24 months-survival	77	25		

Statistical analyses

Statistical analysis title	Cox proportional regression
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Statistical analysis description:

Estimates of the treatment effect was expressed by the hazard ratio including confidence intervals estimated through a Cox proportional regression model and considering the MRD status at randomization as stratification factor.

Comparison groups	Placebo v Lenalidomide
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Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.379

Secondary: Progression-free survival according to Investigator's assessment

End point title	Progression-free survival according to Investigator's assessment
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End point description:

Because for the median progression free survival the upper range of the 95% confidence interval was not estimable, the progression rates (percentages, rounded to the nearest whole number) at 12, 24, 36, 48 and 60 months are given. The median progression free survival was 14.6 months (95% Confidence interval 10.3 months - 23.3 months) for the placebo group and 42.8 months (35.0 months - not estimable) for the lenalidomide group. $P < 0.001$ (by log-rank test stratified by MRD Status at randomization).

End point type	Secondary
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End point timeframe:

This analysis was done at a median observation time of 68.3 months (IQR: 53.4-82.6).

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	29		
Units: percentage				
12 months-survival	91	55		
24 months-survival	75	30		
36 months-survival	61	15		
48 months-survival	47	7		
60 months-survival	47	7		

Statistical analyses

Statistical analysis title	Cox proportional regression
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Statistical analysis description:

Estimates of the treatment effect was expressed by the hazard ratio including confidence intervals estimated through a Cox proportional regression model and considering the MRD status at randomization as stratification factor.

Comparison groups	Placebo v Lenalidomide
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Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.327

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
The median overall survival for the placebo group was not reached and 93.5 months for the lenalidomide group. Therefore overall survival rates (percentages, rounded to the nearest whole number) at 12, 24, 36, 48 and 60 months are given. P=0.185 (by log-rank test, non-stratified).	
End point type	Secondary
End point timeframe:	
This analysis was done at a median observation time of 68.2 months (IQR: 53.4 months - 82.6 months).	

End point values	Lenalidomide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	29		
Units: percentages				
12 months survival	100	93		
24 months survival	95	93		
36 months survival	91	93		
48 months survival	85	88		
60 months survival	78	88		

Statistical analyses

Statistical analysis title	Cox proportional regression
Statistical analysis description:	
Estimates of the treatment effect was expressed by the hazard ratio including confidence intervals estimated through a Cox proportional regression model.	
Comparison groups	Lenalidomide v Placebo

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.194
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	6.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Lenalidomide
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Reporting group description: -

Serious adverse events	Placebo	Lenalidomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)	34 / 60 (56.67%)	
number of deaths (all causes)	4	16	
number of deaths resulting from adverse events	1	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia	Additional description: Acute lymphocytic leukaemia		
subjects affected / exposed	0 / 29 (0.00%)	4 / 60 (6.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma	Additional description: Basal cell carcinoma		
subjects affected / exposed	2 / 29 (6.90%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease	Additional description: Bowen's disease		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the duodenum	Additional description: Carcinoid tumour of the duodenum		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma	Additional description: Clear cell renal cell carcinoma		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma unspecified histology indolent	Additional description: Non-Hodgkin's lymphoma unspecified histology indolent		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma	Additional description: Oesophageal adenocarcinoma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer	Additional description: Prostate cancer		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma	Additional description: Prostatic adenoma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma	Additional description: Renal cell carcinoma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin papilloma	Additional description: Skin papilloma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		

subjects affected / exposed	1 / 29 (3.45%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung	Additional description: Squamous cell carcinoma of lung		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of skin	Additional description: Squamous cell carcinoma of skin		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma	Additional description: Thyroid adenoma		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease	Additional description: Peripheral arterial occlusive disease		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Oesophageal operation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Oesophageal operation		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
General disorders and administration site conditions Death subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Death		
	0 / 29 (0.00%)	2 / 60 (3.33%)	
	0 / 0	0 / 2	
	0 / 0	0 / 2	
General physical health deterioration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: General physical health deterioration		
	0 / 29 (0.00%)	2 / 60 (3.33%)	
	0 / 0	0 / 3	
	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pleural effusion		
	1 / 29 (3.45%)	1 / 60 (1.67%)	
	0 / 1	0 / 1	
	0 / 0	0 / 0	
Pulmonary embolism subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pulmonary embolism		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	1 / 1	
	0 / 0	0 / 0	
Psychiatric disorders Korsakoff's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Korsakoff's syndrome		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Investigations Catheterisation cardiac subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Catheterisation cardiac		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Infusion related reaction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Infusion related reaction		
	1 / 29 (3.45%)	0 / 60 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Radius fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Radius fracture		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Tendon rupture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Tendon rupture		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	1 / 1	
	0 / 0	0 / 0	
Thermal burn subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Thermal burn		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Congenital, familial and genetic disorders Hamartoma subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Hamartoma		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Cardiac disorders Acute myocardial infarction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Acute myocardial infarction		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Atrial fibrillation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Atrial fibrillation		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	1 / 1	
	0 / 0	0 / 0	
Cardiac disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Cardiac disorder		
	0 / 29 (0.00%)	1 / 60 (1.67%)	
	0 / 0	0 / 1	
	0 / 0	0 / 1	

Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis	Additional description: Coronary artery stenosis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence	Additional description: Mitral valve incompetence		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence	Additional description: Tricuspid valve incompetence		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial nerve disorder	Additional description: Facial nerve disorder		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	2 / 29 (6.90%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: Transient ischaemic attack		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
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			
Autoimmune haemolytic anaemia	Additional description: Autoimmune haemolytic anaemia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
subjects affected / exposed	2 / 29 (6.90%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Extraocular muscle paresis	Additional description: Extraocular muscle paresis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
	Additional description: Dental caries		

subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus	Additional description: Mechanical ileus		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis	Additional description: Oesophageal stenosis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute	Additional description: Cholecystitis acute		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic	Additional description: Cholecystitis chronic		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Precancerous skin lesion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome	Additional description: Rotator cuff syndrome		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis	Additional description: Bronchitis		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia	Additional description: Bronchopneumonia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis	Additional description: Bronchopulmonary aspergillosis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellutis	Additional description: Cellutis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial	Additional description: Endocarditis bacterial		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epididymitis	Additional description: Epididymitis		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	2 / 29 (6.90%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection	Additional description: Gastrointestinal infection		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis E	Additional description: Hepatitis E		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection	Additional description: Lung infection		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia	Additional description: Pneumocystis jirovecii pneumonia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	2 / 29 (6.90%)	6 / 60 (10.00%)	
occurrences causally related to treatment / all	1 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy	Additional description: Progressive multifocal leukoencephalopathy		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonas bronchitis	Additional description: Pseudomonas bronchitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis	Additional description: Pulmonary sepsis		
subjects affected / exposed	1 / 29 (3.45%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic arthritis staphylococcal	Additional description: Septic arthritis staphylococcal		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Septic shock		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal	Additional description: Wound infection staphylococcal		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
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: 0 %

Non-serious adverse events	Placebo	Lenalidomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 29 (75.86%)	55 / 60 (91.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: Basal cell carcinoma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Squamous cell carcinoma of skin	Additional description: Squamous cell carcinoma of skin		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Tumour flare	Additional description: Tumour flare		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	1	2	
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	1 / 29 (3.45%)	2 / 60 (3.33%)	
occurrences (all)	1	2	
Haemorrhage	Additional description: Haemorrhage		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Hot flush	Additional description: Hot flush		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	2 / 29 (6.90%)	2 / 60 (3.33%)	
occurrences (all)	3	2	
Peripheral arterial occlusive disease	Additional description: Peripheral arterial occlusive disease		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Thrombosis	Additional description: Thrombosis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Inguinal hernia repair	Additional description: Inguinal hernia repair		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Ligament operation	Additional description: Ligament operation		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Nasal septal operation	Additional description: Nasal septal operation		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Surgery	Additional description: Surgery		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	2 / 29 (6.90%)	4 / 60 (6.67%)	
occurrences (all)	2	5	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 29 (3.45%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	7 / 29 (24.14%)	16 / 60 (26.67%)	
occurrences (all)	11	31	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	0 / 29 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	0 / 29 (0.00%)	5 / 60 (8.33%)	
occurrences (all)	0	7	
Malaise	Additional description: Malaise		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Mucosal dryness	Additional description: Mucosal dryness		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	0 / 29 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	4	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	1 / 29 (3.45%)	2 / 60 (3.33%)	
occurrences (all)	1	2	
Pain	Additional description: Pain		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	1	1	
Performance status decreased	Additional description: Performance status decreased		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling	Additional description: Peripheral swelling		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 29 (3.45%)	5 / 60 (8.33%)	
occurrences (all)	2	10	
Swelling	Additional description: Swelling		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Thirst decreased	Additional description: Thirst decreased		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Immune system disorders			
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Balanoposthitis	Additional description: Balanoposthitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Erectile dysfunction	Additional description: Erectile dysfunction		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Genital tract inflammation	Additional description: Genital tract inflammation		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Nipple pain	Additional description: Nipple pain		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease	
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	2
Cough	Additional description: Cough	
subjects affected / exposed	3 / 29 (10.34%)	13 / 60 (21.67%)
occurrences (all)	6	18
Dysphonia	Additional description: Dysphonia	
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)
occurrences (all)	1	1
Dyspnoea	Additional description: Dyspnoea	
subjects affected / exposed	1 / 29 (3.45%)	7 / 60 (11.67%)
occurrences (all)	1	7
Dyspnoea exertional	Additional description: Dyspnoea exertional	
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	2
Epistaxis	Additional description: Epistaxis	
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	2
Hiccups	Additional description: Hiccups	
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	1
Nasal congestion	Additional description: Nasal congestion	
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	2
Nasal dryness	Additional description: Nasal dryness	
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	1
Oropharyngeal pain	Additional description: Oropharyngeal pain	
subjects affected / exposed	2 / 29 (6.90%)	0 / 60 (0.00%)
occurrences (all)	3	0
Productive cough	Additional description: Productive cough	
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	1
Respiratory tract infection viral	Additional description: Respiratory tract infection viral	

subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic	Additional description: Rhinitis allergic		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation	Additional description: Agitation		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Depression	Additional description: Depression		
subjects affected / exposed	0 / 29 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	6	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	0 / 29 (0.00%)	6 / 60 (10.00%)	
occurrences (all)	0	7	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Stress	Additional description: Stress		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Investigations			
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	0 / 29 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	6	
Electrocardiogram QT prolonged	Additional description: Electrocardiogram QT prolonged		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	2	
Electrocardiogram ST segment depression	Additional description: Electrocardiogram ST segment depression		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		

subjects affected / exposed	0 / 29 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	4	
Haemoglobin	Additional description: Haemoglobin		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Liver function test increased	Additional description: Liver function test increased		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	2	
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	1	1	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	0 / 29 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Weight increased	Additional description: Weight increased		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Contusion	Additional description: Contusion		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	1	1	
Epicondylitis	Additional description: Epicondylitis		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	2	0	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Ligament sprain	Additional description: Ligament sprain		

subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 60 (0.00%) 0	
Cardiac disorders			
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 60 (3.33%) 2	
Sinus bradycardia	Additional description: Sinus bradycardia		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 60 (3.33%) 2	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1	
Nervous system disorders			
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1	
Dizziness	Additional description: Dizziness		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	3 / 60 (5.00%) 3	
Dysaesthesia	Additional description: Dysaesthesia		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1	
Headache	Additional description: Headache		
subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	7 / 60 (11.67%) 11	
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 60 (3.33%) 2	
Intention tremor	Additional description: Intention tremor		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1	
Migraine	Additional description: Migraine		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	2	
Muscle spasticity	Additional description: Muscle spasticity		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	2	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy	Additional description: Peripheral motor neuropathy		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	1 / 29 (3.45%)	5 / 60 (8.33%)	
occurrences (all)	1	5	
Presyncope	Additional description: Presyncope		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 29 (3.45%)	4 / 60 (6.67%)	
occurrences (all)	1	4	

Aplastic anaemia subjects affected / exposed occurrences (all)	Additional description: Aplastic anaemia	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Granulocytopenia subjects affected / exposed occurrences (all)	Additional description: Granulocytopenia	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Histiocytosis haematophagic subjects affected / exposed occurrences (all)	Additional description: Histiocytosis haematophagic	
	1 / 29 (3.45%) 1	0 / 60 (0.00%) 0
Leukopenia subjects affected / exposed occurrences (all)	Additional description: Leukopenia	
	2 / 29 (6.90%) 3	9 / 60 (15.00%) 17
Lymphadenopathy subjects affected / exposed occurrences (all)	Additional description: Lymphadenopathy	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Neutropenia subjects affected / exposed occurrences (all)	Additional description: Neutropenia	
	2 / 29 (6.90%) 3	20 / 60 (33.33%) 44
Thrombocytopenia subjects affected / exposed occurrences (all)	Additional description: Thrombocytopenia	
	0 / 29 (0.00%) 0	6 / 60 (10.00%) 8
Ear and labyrinth disorders		
	Additional description: Deafness	
Deafness subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Ear pain	
Ear pain subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Hypoacusis	
Hypoacusis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Tinnitus	
Tinnitus subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Vertigo	
Vertigo		

subjects affected / exposed	2 / 29 (6.90%)	2 / 60 (3.33%)	
occurrences (all)	2	2	
Vertigo positional	Additional description: Vertigo positional		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Eye disorders			
Abnormal sensation in eye	Additional description: Abnormal sensation in eye		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage	Additional description: Conjunctival haemorrhage		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Dry eye	Additional description: Dry eye		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Eye haemorrhage	Additional description: Eye haemorrhage		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Eye inflammation	Additional description: Eye inflammation		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Macular degeneration	Additional description: Macular degeneration		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Ocular hyperaemia	Additional description: Ocular hyperaemia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Retinal detachment	Additional description: Retinal detachment		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Visual acuity reduced	Additional description: Visual acuity reduced		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 29 (3.45%)	2 / 60 (3.33%)	
occurrences (all)	1	4	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	0 / 29 (0.00%)	5 / 60 (8.33%)	
occurrences (all)	0	5	
Anal fissure	Additional description: Anal fissure		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Aphthous stomatitis	Additional description: Aphthous stomatitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Colitis	Additional description: Colitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Constipation	Additional description: Constipation		
subjects affected / exposed	2 / 29 (6.90%)	14 / 60 (23.33%)	
occurrences (all)	2	15	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 29 (6.90%)	25 / 60 (41.67%)	
occurrences (all)	4	49	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	1 / 29 (3.45%)	3 / 60 (5.00%)	
occurrences (all)	1	5	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Faeces soft	Additional description: Faeces soft		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Flatulence	Additional description: Flatulence		

subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	1	1	
Gastritis	Additional description: Gastritis		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Gastritis erosive	Additional description: Gastritis erosive		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Loose tooth	Additional description: Loose tooth		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Nausea	Additional description: Nausea		
subjects affected / exposed	3 / 29 (10.34%)	5 / 60 (8.33%)	
occurrences (all)	3	7	
Oral cavity fistula	Additional description: Oral cavity fistula		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Periodontal disease	Additional description: Periodontal disease		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Toothache	Additional description: Toothache		

subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Biliary colic	Additional description: Biliary colic		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne	Additional description: Acne		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Angioedema	Additional description: Angioedema		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	1 / 29 (3.45%)	4 / 60 (6.67%)	
occurrences (all)	2	5	
Eczema	Additional description: Eczema		
subjects affected / exposed	1 / 29 (3.45%)	2 / 60 (3.33%)	
occurrences (all)	1	2	
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	2	1	
Hyperhidrosis	Additional description: Hyperhidrosis		

subjects affected / exposed	0 / 29 (0.00%)	5 / 60 (8.33%)	
occurrences (all)	0	10	

Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

Night sweats	Additional description: Night sweats		
subjects affected / exposed	1 / 29 (3.45%)	3 / 60 (5.00%)	
occurrences (all)	1	12	

Petechiae	Additional description: Petechiae		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

Pruritus	Additional description: Pruritus		
subjects affected / exposed	2 / 29 (6.90%)	8 / 60 (13.33%)	
occurrences (all)	3	15	

Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	

Pruritus generalised	Additional description: Pruritus generalised		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	

Rash	Additional description: Rash		
subjects affected / exposed	5 / 29 (17.24%)	17 / 60 (28.33%)	
occurrences (all)	6	35	

Rosacea	Additional description: Rosacea		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	

Skin disorder	Additional description: Skin disorder		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

Skin reaction	Additional description: Skin reaction		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

Skin irritation	Additional description: Skin irritation		

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Toxic epidermal necrolysis	Additional description: Toxic epidermal necrolysis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Glomerulonephritis minimal lesion	Additional description: Glomerulonephritis minimal lesion		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Polyuria	Additional description: Polyuria		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	1 / 29 (3.45%)	10 / 60 (16.67%)	
occurrences (all)	1	15	
Back pain	Additional description: Back pain		
subjects affected / exposed	2 / 29 (6.90%)	6 / 60 (10.00%)	
occurrences (all)	2	6	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	3	
Bursitis	Additional description: Bursitis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	2	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	2 / 29 (6.90%)	1 / 60 (1.67%)	
occurrences (all)	2	1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	3 / 29 (10.34%)	9 / 60 (15.00%)	
occurrences (all)	4	23	
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		

subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	1 / 29 (3.45%)	1 / 60 (1.67%)	
occurrences (all)	1	1	
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	0 / 29 (0.00%)	5 / 60 (8.33%)	
occurrences (all)	0	10	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	0 / 29 (0.00%)	2 / 60 (3.33%)	
occurrences (all)	0	2	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	2 / 29 (6.90%)	7 / 60 (11.67%)	
occurrences (all)	2	10	
Polyarthritis	Additional description: Polyarthritis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Spinal pain	Additional description: Spinal pain		
subjects affected / exposed	1 / 29 (3.45%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Tendon discomfort	Additional description: Tendon discomfort		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	2	
Infections and infestations			
Abscess limb	Additional description: Abscess limb		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Atypical pneumonia	Additional description: Atypical pneumonia		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	2 / 29 (6.90%)	9 / 60 (15.00%)	
occurrences (all)	2	13	

Bronchopneumonia subjects affected / exposed occurrences (all)	Additional description: Bronchopneumonia	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	Additional description: Conjunctivitis	
	1 / 29 (3.45%) 1	0 / 60 (0.00%) 0
Cystitis subjects affected / exposed occurrences (all)	Additional description: Cystitis	
	1 / 29 (3.45%) 1	1 / 60 (1.67%) 3
Ear infection subjects affected / exposed occurrences (all)	Additional description: Ear infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 2
Febrile infection subjects affected / exposed occurrences (all)	Additional description: Febrile infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Fungal skin infection subjects affected / exposed occurrences (all)	Additional description: Fungal skin infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	Additional description: Gastroenteritis	
	1 / 29 (3.45%) 1	0 / 60 (0.00%) 0
Gastrointestinal infection subjects affected / exposed occurrences (all)	Additional description: Gastrointestinal infection	
	0 / 29 (0.00%) 0	2 / 60 (3.33%) 2
Herpes virus infection subjects affected / exposed occurrences (all)	Additional description: Herpes virus infection	
	0 / 29 (0.00%) 0	2 / 60 (3.33%) 4
Herpes zoster subjects affected / exposed occurrences (all)	Additional description: Herpes zoster	
	0 / 29 (0.00%) 0	2 / 60 (3.33%) 2
Infected dermal cyst subjects affected / exposed occurrences (all)	Additional description: Infected dermal cyst	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Infection subjects affected / exposed occurrences (all)	Additional description: Infection	
	1 / 29 (3.45%) 1	2 / 60 (3.33%) 3

Influenza subjects affected / exposed occurrences (all)	Additional description: Influenza	
	1 / 29 (3.45%)	1 / 60 (1.67%)
	1	1
Laryngitis subjects affected / exposed occurrences (all)	Additional description: Laryngitis	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1
Mucosal infection subjects affected / exposed occurrences (all)	Additional description: Mucosal infection	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: Nasopharyngitis	
	9 / 29 (31.03%)	20 / 60 (33.33%)
	17	51
Neutropenic infection subjects affected / exposed occurrences (all)	Additional description: Neutropenic infection	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1
Oral candidiasis subjects affected / exposed occurrences (all)	Additional description: Oral candidiasis	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1
Oral herpes subjects affected / exposed occurrences (all)	Additional description: Oral herpes	
	1 / 29 (3.45%)	3 / 60 (5.00%)
	1	4
Otitis media subjects affected / exposed occurrences (all)	Additional description: Otitis media	
	0 / 29 (0.00%)	2 / 60 (3.33%)
	0	2
Paronychia subjects affected / exposed occurrences (all)	Additional description: Paronychia	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	2
Parotitis subjects affected / exposed occurrences (all)	Additional description: Parotitis	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1
Periodontitis subjects affected / exposed occurrences (all)	Additional description: Periodontitis	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1
Pharyngitis subjects affected / exposed occurrences (all)	Additional description: Pharyngitis	
	0 / 29 (0.00%)	1 / 60 (1.67%)
	0	1

Pneumonia subjects affected / exposed occurrences (all)	Additional description: Pneumonia	
	0 / 29 (0.00%) 0	2 / 60 (3.33%) 3
Respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Respiratory tract infection	
	1 / 29 (3.45%) 1	5 / 60 (8.33%) 5
Rhinitis subjects affected / exposed occurrences (all)	Additional description: Rhinitis	
	1 / 29 (3.45%) 1	5 / 60 (8.33%) 8
Rhinovirus infection subjects affected / exposed occurrences (all)	Additional description: Rhinovirus infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Septic shock subjects affected / exposed occurrences (all)	Additional description: Septic shock	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Sinusitis subjects affected / exposed occurrences (all)	Additional description: Sinusitis	
	1 / 29 (3.45%) 2	1 / 60 (1.67%) 1
Skin infection subjects affected / exposed occurrences (all)	Additional description: Skin infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Superinfection subjects affected / exposed occurrences (all)	Additional description: Superinfection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Tonsillitis subjects affected / exposed occurrences (all)	Additional description: Tonsillitis	
	1 / 29 (3.45%) 1	1 / 60 (1.67%) 1
Tooth infection subjects affected / exposed occurrences (all)	Additional description: Tooth infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Upper respiratory tract infection	
	4 / 29 (13.79%) 5	9 / 60 (15.00%) 11
Varicella zoster virus infection subjects affected / exposed occurrences (all)	Additional description: Varicella zoster virus infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1

Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection	
	1 / 29 (3.45%) 1	1 / 60 (1.67%) 1
Viral infection subjects affected / exposed occurrences (all)	Additional description: Viral infection	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
Metabolism and nutrition disorders		
	Additional description: Decreased appetite	
	1 / 29 (3.45%) 1	1 / 60 (1.67%) 1
	Additional description: Diabetes mellitus	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Fructose intolerance	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Gout	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Hypercreatininaemia	
	1 / 29 (3.45%) 1	0 / 60 (0.00%) 0
	Additional description: Hyperuricaemia	
	1 / 29 (3.45%) 2	0 / 60 (0.00%) 0
	Additional description: Hypokalaemia	
	0 / 29 (0.00%) 0	3 / 60 (5.00%) 3
	Additional description: Hypomagnesaemia	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Hypophosphataemia	
	0 / 29 (0.00%) 0	1 / 60 (1.67%) 1
	Additional description: Iron deficiency	

subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Magnesium deficiency	Additional description: Magnesium deficiency		
subjects affected / exposed	0 / 29 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2014	<p>The additional information on lenalidomide in the Investigator's Brochure version 16 was included in both the protocol and the patient information. The inclusion criteria were adapted to the new recommendations after detailed discussion regarding hepatitis screening. The exclusion criteria with regard to the history of other malignant diseases were changed, as we have current figures from a study with a total of 450 patients that show no increased incidence of secondary malignancies under lenalidomide.</p> <p>In order to facilitate the inclusion of patients, pre-screening can now also be dispensed with completely. Inclusion is possible if the patients can nevertheless be clearly assigned to the high-risk population (definition remains unchanged). Corresponding information was included in the protocol, the patient information and the overviews of the study (flow charts). The time points of the study, which were changed due to the delayed recruitment, were adjusted.</p>
06 August 2014	<p>The reason for this amendment is the additional information on lenalidomide in the Investigator's Brochure version 17, which has been included in the patient information:</p> <ul style="list-style-type: none">- Sleep disturbances- Effects on the ability to drive <p>In addition to the amended version of the Patient Information and Consent, we have prepared an addendum for patients who have already been randomised.</p>
15 December 2015	<p>Due to the slow recruitment, we had to assume that the CLLM1 study will not finish recruiting.</p> <p>In order to best evaluate the data of this study so far, we have implemented an interim analysis.</p> <p>Furthermore, the pre-screening was cancelled in order to simplify the study procedure and to save costs. The last pre-screened patient will be screened and, if necessary, randomised in March 2016 at the latest. We will also close recruitment at this time.</p> <p>Until then, centres will only be able to screen patients after the firstline. The MRD analysis and any available laboratory findings on cytogenetics will continue to be used for stratification.</p>
04 July 2016	<p>The updated Investigator's Brochure, version 19, dated 21 April 2016, contains new information on adverse reactions to the test substance lenalidomide, as listed below:</p> <p>Side effects that occurred in 10% or more patients: Abnormal liver function tests</p> <p>Side effects that occurred in 1% to 10% of patients: Hypothyroidism</p> <p>Previously, an incidence of 1%-10% was given for abnormal liver function tests; hypothyroidism was not previously listed.</p> <p>Accordingly, an addendum to the German patient information was written. Patients under therapy or in follow-up are informed about the new information and asked for their written consent.</p> <p>Furthermore, there have been changes in the supply chain of the placebo manufacturer for the study: the manufacturer's name has been changed from AAI to Alcamì.</p>

20 December 2016	<p>The amendment includes the implementation of the recommendation of the DSMB, decided at the DSMB meeting on 17 June 2016. (See also attachment 1, certificate of non objection) The DSMB discussed the results of the first planned interim analysis and concluded that there are still no safety concerns about continuing the study. The DSMB assessed the results of the interim analysis as robust and statistically significant for the lenalidomide arm and recommended unblinding the study. The Amendment History contains the results of the interim analysis in more detail and in the form of the abstract submitted to the ASH. The supply of study medication will be changed to an IDOS system in the new year and will be supplied unblinded with a new label. As no more study patients are receiving protocol allopurinol, the supply for this drug has been discontinued. Please note the simultaneous submission of the new Investigator's Brochure. The updated Investigator's Brochure, version 20 of 06 July 2016 does not contain any new side effects of the test substance lenalidomide.</p>
23 November 2017	<p>The amendment includes the change of the patient information and consent form in the form of an addendum due to the changes in the current version 21 of the Investigator's Brochure for lenalidomide, prepared on 24 April 2017.</p> <p>Two previously unknown adverse reactions were described in IB version 21:</p> <ul style="list-style-type: none"> - DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome: This drug reaction includes skin reactions such as redness, peeling, also increase in eosinophils, fever, swollen lymph nodes, organ complications such as hepatitis, pneumonitis, nephritis, myocarditis or pericarditis. - T-cell-like acute leukaemia <p>Other changes in the new IB relate to wording and formatting only - the changes have no impact on data or information.</p> <p>Both adverse reactions were included in the patient information addendum.</p>
21 December 2017	<p>The amendment includes the change of the patient information and consent form in the form of an addendum due to the changes in the current version 21 of the Investigator's Brochure for lenalidomide and information on the end of treatment with the study therapy lenalidomide. There are no changes for the patient information from the Investigator's Brochure version 22.</p> <p>As described in our Amendment 6 letter of 25.10.2017, two previously unknown adverse reactions were described in IB version 21 (DRESS, T-cell like Acute Leukaemia). Both side effects from Investigator's Brochure version 21 as well as the information about the end of treatment with lenalidomide (see letter of 30.11.2017) were included in Addendum 9 to the patient information of 07.12.2017.</p> <p>Version 22 of the Investigator's Brochure for lenalidomide was issued on 03.11.2017. The following changes were made to the organ class "Infections and Infestations":</p> <ul style="list-style-type: none"> - The non-specific description "bacterial, viral and fungal infections" (including opportunistic infections) with the frequency "very common" was replaced by more specific and detailed descriptions (see screenshot). <p>Even taking into account the more detailed side effects described, the risk-benefit assessment of the CLLM1 study remains unchanged. There is no reason to amend the patient information in this regard, as the more detailed descriptions and a reassessment of the frequency of events (some infections are less frequent than 10%) are not relevant in our opinion. The fact that CLL patients have an increased risk of infection anyway was already described in the current patient information version 5.0 of 20.10.2015.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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15 November 2017	<p>Randomization has been closed early in March 2016 because of slow recruitment. 468 patients were screened for eligibility and a total of 89 patients had been randomised for the study. Two formal interim analyses have been subsequently planned when 20% (24 events) and 41% (48 events) of the total 118 PFS events have been observed. Both interim analyses were designed to decide whether the study might be stopped early for either efficacy or futility. The results of the first interim analysis were statistically significant, robust and reliable with regard to the pre-specified stopping boundaries given by the Hwang-Shih-DeCani spending function. Based on these results, DSMB concluded that the stopping boundary for efficacy has been surpassed and, as such, recommended that the subjects should be unblinded. All patients should be further observed and patients in the lenalidomide arm should continue with the treatment. The further observation of the subjects in the study has the objective to collect further safety data and data for the secondary endpoints. Concerning future analyses, the second interim analysis will be omitted and the final analysis will be conducted either as soon as all patients have experienced disease progression or at the end of the study.</p> <p>Four cases of acute lymphoblastic leukemia were reported in the LEN arm (no cases in the placebo arm). After the occurrence of the second case, the study treatment was early discontinued for all patients in November 2017</p>	-
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Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In view of four unexpected ALL cases observed in the LEN group, maintenance with LEN in high risk CLL cannot be recommended as maintenance therapy in CLL.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28916311>

<http://www.ncbi.nlm.nih.gov/pubmed/33512465>