# 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 |

### 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 ≥10-2 or a combination of MRD levels of ≥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 responsed to first-line chemoimmunotherapy, and a high risk for early progression defined as a MRD level in the peripheral blood of ≥10−2 (1 in 100 cells) or a combination of MRD levels of ≥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 personal, 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 ≥ 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 ≥ 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<br>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<br>Units: years | | | |
| median | 64 | 64 | |
| inter-quartile range (Q1-Q3) | 57.3 to 69.8 | 58.0 to 69.5 | - |
| Gender categorical<br>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<br>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 β2-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 |

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 |

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 |
|---|---|

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 |

| | |
|---|---|
| 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 |

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 |

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 |
|---|---|

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 |

| | |
|---|---|
| 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description: -

| | |
|---|---|
| Reporting group title | Lenalidomide |

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

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|---|---|---|---|
| Infusion related reaction | Additional description: Infusion related reaction | | |
| 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 | |
| Radius fracture | Additional description: Radius fracture | | |
| 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 | |
| Tendon rupture | Additional description: Tendon rupture | | |
| 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 | |
| Thermal burn | Additional description: Thermal burn | | |
| 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 | |
| Congenital, familial and genetic disorders | | | |
| Hamartoma | Additional description: Hamartoma | | |
| 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 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | Additional description: Acute myocardial infarction | | |
| 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 | |
| Atrial fibrillation | Additional description: Atrial fibrillation | | |
| 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 | |
| Cardiac disorder | Additional description: Cardiac 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 / 1 | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | Additional description: 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 | Additional description: 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | Additional description: 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 | Additional description: 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 | Additional description: 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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

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|---|---|---|---|
| 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 | |

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

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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

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

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

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

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|---|---|---|---|
| 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 | 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.<br>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).<br>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. |
| 06 August 2014 | 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:<br>- Sleep disturbances<br>- Effects on the ability to drive<br>In addition to the amended version of the Patient Information and Consent, we have prepared an addendum for patients who have already been randomised. |
| 15 December 2015 | Due to the slow recruitment, we had to assume that the CLLM1 study will not finish recruiting.<br>In order to best evaluate the data of this study so far, we have implemented an interim analysis.<br>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.<br>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. |
| 04 July 2016 | 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:<br>Side effects that occurred in 10% or more patients: Abnormal liver function tests<br><br>Side effects that occurred in 1% to 10% of patients: Hypothyroidism<br>Previously, an incidence of 1%-10% was given for abnormal liver function tests; hypothyroidism was not previously listed.<br>Accordingly, an addendum to the German patient information was written.<br>Patients under therapy or in follow-up are informed about the new information and asked for their written consent.<br>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 Alcami. |

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| 20 December 2016 | 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.<br>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.<br>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. |
| 23 November 2017 | 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.<br>Two previously unknown adverse reactions were described in IB version 21:<br>- 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.<br>- T-cell-like acute leukaemia<br>Other changes in the new IB relate to wording and formatting only - the changes have no impact on data or information.<br>Both adverse reactions were included in the patient information addendum. |
| 21 December 2017 | 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.<br>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 Invesitigator`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.<br>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":<br>- 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).<br><br>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. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|

| | | |
|---|---|---|
| 15 November 2017 | 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.<br>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 | - |

Notes:

## Limitations and caveats

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

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| 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