Clinical trial results:
A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia
A Companion Trial to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Summary

EudraCT number	2011-006293-72
Trial protocol	GB IT DE
Global end of trial date	29 June 2018

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-312-0117

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01539291
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2018
Global end of trial reached?	Yes
Global end of trial date	29 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study (GS-US-312-0117) that is a companion study to Study GS-US-312-0116 (2011-005180-24), is to evaluate the effect of idelalisib (IDL) on the onset, magnitude, and duration of tumor control in participants with previously treated Chronic Lymphocytic Leukemia (CLL).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.
This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	United States: 148
Worldwide total number of subjects	196
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	44
From 65 to 84 years	146
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and Europe. The first participant was screened on 03 October 2012. The last study visit occurred on 29 June 2018.

Pre-assignment

Screening details:

Participants must have been enrolled in Gilead-sponsored Study GS-US-312-0116 (2011-005180-24) to be eligible to continued access to IDL in this study.

Period 1

Period 1 title	Study GS-US-312-0116
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	IDL+R to IDL

Arm description:

Participants received IDL 150 mg tablet twice daily plus rituximab (R) (8 infusions intravenously) in Study GS-US-312-0116 and may have entered Study GS-US-312-0117 to receive IDL 150 mg or 300 mg tablet twice daily. Due to the small number of participants in the IDL+R (PD) to IDL 300 mg group, data from this group were combined with the IDL+R to IDL 150 mg group for Baseline Characteristics and Endpoints sections.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL 101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg or 300 mg tablet(s) administered orally twice daily

Arm title	Placebo+R (PD) to IDL 150 mg

Arm description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of progressive disease (PD) and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL 101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg tablet administered orally twice daily

Arm title	Placebo+R to IDL 150 mg

Arm description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-

US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL 101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg tablet administered orally twice daily

Number of subjects in period 1	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg
Started	110	42	44
Completed	85	42	44
Not completed	25	0	0
Physician decision	1	-	-
Adverse Event	9	-	-
Withdrawal by Subject	12	-	-
Unspecified	1	-	-
Study Terminated by Sponsor	2	-	-

Period 2

Period 2 title	Study GS-US-312-0117
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	IDL+R to IDL

Arm description:

Participants received IDL 150 mg tablet twice daily plus rituximab (R) (8 infusions intravenously) in Study GS-US-312-0116 and may have entered Study GS-US-312-0117 to receive IDL 150 mg or 300 mg tablet twice daily.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL 101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg or 300 mg tablet(s) administered orally twice daily

Arm title	Placebo+R (PD) to IDL 150 mg

Arm description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of PD and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL 101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg tablet administered orally twice daily

Arm title	Placebo+R to IDL 150 mg

Arm description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL 101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg tablet administered orally twice daily

Number of subjects in period 2[1]	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg
Started	75	42	44
Completed	32	20	18
Not completed	43	22	26
Physician decision	9	6	4
Adverse Event	23	9	12
Withdrawal by Subject	5	6	4
Unspecified	3	1	1
Study Terminated by Sponsor	3	-	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Participant Started in Period 2 (Study GS-US-312-0117) = Completed GS-US-312-0116 and Enrolled in GS-US-312-0117.

Baseline characteristics

Reporting groups	
Reporting group title	IDL+R to IDL

Reporting group description:

Participants received IDL 150 mg tablet twice daily plus rituximab (R) (8 infusions intravenously) in Study GS-US-312-0116 and may have entered Study GS-US-312-0117 to receive IDL 150 mg or 300 mg tablet twice daily. Due to the small number of participants in the IDL+R (PD) to IDL 300 mg group, data from this group were combined with the IDL+R to IDL 150 mg group for Baseline Characteristics and Endpoints sections.

Reporting group title	Placebo+R (PD) to IDL 150 mg

Reporting group description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of progressive disease (PD) and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group title	Placebo+R to IDL 150 mg

Reporting group description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg
Number of subjects	110	42	44
Age categorical Units: Subjects			
< 65 years	21	13	10
≥ 65 years	89	29	34
Age continuous Units: years			
arithmetic mean	71	69	70
standard deviation	± 7.7	± 8.2	± 8.4
Gender categorical Units: Subjects			
Female	34	11	18
Male	76	31	26
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	1
Not Hispanic or Latino	101	39	42
Not Permitted	6	2	1
Race Units: Subjects			
White	100	37	40
Black or African American	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Other	2	2	0
Not Permitted	5	3	1

17p Deletion and/ or TP53 Mutation Status Units: Subjects			
Either	46	21	14
Neither	64	21	30
Immunoglobulin heavy chain variable region (IgHV) Mutation Status Units: Subjects			
Mutated	19	6	7
Unmutated	91	36	37
Karnofsky Performance Status (KPS)			
KPS is a tool used to measure the ability to perform ordinary tasks. The score ranges from 0 to 100, with a higher score indicating that the participant is better able to carry out daily activities.			
Units: Subjects			
KPS = 40	1	0	0
KPS = 50	3	1	0
KPS = 60	6	2	0
KPS = 70	20	4	4
KPS = 80	42	19	20
KPS = 90	23	12	12
KPS = 100	15	4	8

Reporting group values	Total		
Number of subjects	196		
Age categorical Units: Subjects			
< 65 years	44		
≥ 65 years	152		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	63		
Male	133		
Ethnicity Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	182		
Not Permitted	9		
Race Units: Subjects			
White	177		
Black or African American	6		
Native Hawaiian or Other Pacific Islander	0		
Asian	0		
American Indian or Alaska Native	0		
Other	4		
Not Permitted	9		
17p Deletion and/ or TP53 Mutation Status			

Units: Subjects			
Either	81		
Neither	115		
Immunoglobulin heavy chain variable region (IgHV) Mutation Status Units: Subjects			
Mutated	32		
Unmutated	164		
Karnofsky Performance Status (KPS)			
KPS is a tool used to measure the ability to perform ordinary tasks. The score ranges from 0 to 100, with a higher score indicating that the participant is better able to carry out daily activities.			
Units: Subjects			
KPS = 40	1		
KPS = 50	4		
KPS = 60	8		
KPS = 70	28		
KPS = 80	81		
KPS = 90	47		
KPS = 100	27		

End points

End points reporting groups

Reporting group title	IDL+R to IDL

Reporting group description:

Participants received IDL 150 mg tablet twice daily plus rituximab (R) (8 infusions intravenously) in Study GS-US-312-0116 and may have entered Study GS-US-312-0117 to receive IDL 150 mg or 300 mg tablet twice daily. Due to the small number of participants in the IDL+R (PD) to IDL 300 mg group, data from this group were combined with the IDL+R to IDL 150 mg group for Baseline Characteristics and Endpoints sections.

Reporting group title	Placebo+R (PD) to IDL 150 mg

Reporting group description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of progressive disease (PD) and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group title	Placebo+R to IDL 150 mg

Reporting group description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group title	IDL+R to IDL

Reporting group description:

Participants received IDL 150 mg tablet twice daily plus rituximab (R) (8 infusions intravenously) in Study GS-US-312-0116 and may have entered Study GS-US-312-0117 to receive IDL 150 mg or 300 mg tablet twice daily.

Reporting group title	Placebo+R (PD) to IDL 150 mg

Reporting group description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of PD and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group title	Placebo+R to IDL 150 mg

Reporting group description:

Participants received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Subject analysis set title	IDL+R
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants were randomized to receive IDL 150 mg tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116.

Subject analysis set title	Placebo+R
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants were randomized to receive placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116.

Subject analysis set title	IDL/Placebo+R to IDL
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IDL 150 mg tablet or placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 (either met or not met the primary endpoint of PD) and may have entered Study GS-US-312-0117 to receive IDL 150 mg or 300 mg tablet twice daily.

Subject analysis set title	IDL+R to IDL 150 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received IDL 150 mg tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Subject analysis set title	IDL+R (PD) to IDL 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IDL 150 mg tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of PD and entered Study GS-US-312-0117 to receive IDL 300 mg tablet twice daily.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[1]

End point description:

PFS was defined as the interval from the start of study therapy to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria other than lymphocytosis alone. PFS was analyzed using Kaplan-Meier (KM) estimates.
Full Analysis Set included participants in the Intent-to-Treat (ITT) Analysis Set (all participants randomized in Study GS-US-312-0116) who received ≥ 1 dose of IDL, with treatment assignments designated according to randomization in Study GS-US-312-0116.

End point type	Primary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	42	44	
Units: months				
median (confidence interval 95%)	20.3 (17.3 to 26.3)	6.9 (4.1 to 10.7)	16.2 (8.8 to 26.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Percentage of Participants With Any Treatment-Emergent Adverse Events (TEAE), ≥ Grade 3 TEAE, Study Drug-Related TEAE, ≥ Grade 3 Study Drug-Related TEAE, Serious TEAE, Study Drug-Related Serious TEAE, and TEAE Leading to Study Drug Discontinuation

End point title	Safety: Percentage of Participants With Any Treatment-Emergent Adverse Events (TEAE), ≥ Grade 3 TEAE, Study Drug-Related TEAE, ≥ Grade 3 Study Drug-Related TEAE, Serious TEAE, Study Drug-Related Serious TEAE, and TEAE Leading to Study Drug Discontinuation[2]

End point description:

TEAEs were defined as events in a given study period that met one of the following criteria:
- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study treatment.
- The continuing adverse events (AEs) diagnosed prior to the start of treatment and worsened in severity grade, or non-serious AEs at baseline which became serious, or AEs resulting in treatment discontinuation after the start of treatment.

The severity of AEs was graded by the investigator according to the common terminology criteria for adverse events (CTCAE), Version 4.03, whenever possible. The relationship of an AE to study drug

(idelalisib) was assessed using clinical judgment by the investigator, describing the event as either unrelated or related. Events for which the investigator did not record relationship to study drug were considered related to study drug.
Participants in the Full Analysis Set were analyzed.

End point type	Primary

End point timeframe:

First IDL dose date in study GS-US-312-0116 or GS-US-312-0117 to last IDL dose date in study GS-US-312-0117 (maximum: 67.3 months) plus 4 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	42	44	
Units: percentage of participants				
number (not applicable)				
Any TEAE	98.2	100.0	97.7	
≥ Grade 3 TEAE	90.9	88.1	90.9	
Study Drug-Related TEAE	68.2	59.5	72.7	
≥ Grade 3 Study Drug-Related TEAE	47.3	45.2	45.5	
Serious TEAE	80.9	81.0	72.7	
Study Drug-Related Serious TEAE	35.5	26.2	29.5	
TEAE Leading to Study Drug Discontinuation	47.3	64.3	50.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants who achieved a complete response (CR) or partial response (PR). The determination of CLL response and progression were based on standardized International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, as specifically modified for this study to reflect current recommendations which considered the mechanism of action of idelalisib and similar drugs.
Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	42	44	
Units: percentage of participants				
number (confidence interval 95%)	85.5 (77.5 to 91.5)	47.6 (32.0 to 63.6)	68.2 (52.4 to 81.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lymph Node Response Rate

End point title	Lymph Node Response Rate

End point description:

Lymph node response rate was defined as the percentage of participants who achieved a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes.
Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	36	43	
Units: percentage of participants				
number (confidence interval 95%)	97.2 (92.0 to 99.4)	77.8 (60.8 to 89.9)	83.7 (69.3 to 93.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) Rate

End point title	Complete Response (CR) Rate

End point description:

CR rate was defined as the percentage of participants who achieved a CR. The determination of CLL response and progression were based on standardized IWCLL criteria, as specifically modified for this study to reflect current recommendations which considered the mechanism of action of idelalisib and similar drugs.
Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	42	44	
Units: percentage of participants				
number (not applicable)	0.9	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR was defined as the time interval from start of study therapy to the first documentation of CR or PR. Participants in the Full Analysis Set who achieved a CR or PR were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	20	30	
Units: months				
median (inter-quartile range (Q1-Q3))	2.1 (1.9 to 3.8)	3.6 (1.9 to 4.0)	2.8 (1.9 to 4.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause. DOR was analyzed using KM estimates. 999 = Too few events to estimate the upper limit of the confidence interval.
Participants in the Full Analysis Set who achieved a CR or PR were analyzed.

End point type	Secondary

End point timeframe:

From first documentation of CR or PR to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	20	30	
Units: months				
median (confidence interval 95%)	21.4 (16.6 to 26.1)	11.0 (3.3 to 999)	17.6 (13.2 to 37.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Percent Change in Lymph Node Area

End point title	Best Percent Change in Lymph Node Area

End point description:

The best percent change from baseline in lymph node area (SPD) was defined as the largest decrease in tumor size during the study. The baseline SPD was the last value prior to the baseline reference date. For the participants who only had increases in tumor size from baseline, the smallest increase was considered as the best change from baseline in SPD.
Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	36	43	
Units: percent change				
median (inter-quartile range (Q1-Q3))	-80.1 (-86.1 to -70.5)	-69.7 (-79.5 to -53.7)	-71.4 (-80.4 to -62.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Splenomegaly Response Rate

End point title	Splenomegaly Response Rate

End point description:

Splenomegaly response rate was defined as the percentage of participants with baseline splenomegaly who achieved an on-study normalization or a 50% decrease (minimum 2 cm) from baseline in the enlargement of the splenic longest vertical dimension (LVD) (by imaging).
Participants in the Full Analysis Set who had splenomegaly at baseline and at least 1 evaluable postbaseline spleen measurement were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	23	24	
Units: percentage of participants				
number (confidence interval 95%)	80.3 (69.5 to 88.5)	47.8 (26.8 to 69.4)	66.7 (44.7 to 84.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatomegaly Response Rate

End point title	Hepatomegaly Response Rate

End point description:

Hepatomegaly response rate was defined as the percentage of participants with baseline hepatomegaly who achieved an on-study normalization or a 50% decrease (minimum 2 cm) from baseline in the hepatic LVD (by imaging).
Participants in the Full Analysis Set who had hepatomegaly at baseline and at least 1 evaluable postbaseline liver measurement were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	22	20	
Units: percentage of participants				
number (confidence interval 95%)	63.0 (48.7 to 75.7)	36.4 (17.2 to 59.3)	30.0 (11.9 to 54.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Lymphocyte Count (ALC) Response Rate

End point title	Absolute Lymphocyte Count (ALC) Response Rate

End point description:

ALC response rate was defined as the percentage of participants with baseline lymphocytosis (ALC ≥ 4 x 10^9 cells/L) who achieved an on-study ALC < 4 x 10^9 cells/L or demonstrated a ≥ 50% decrease in ALC from baseline; ALC values within 4 weeks post-baseline were excluded from the ALC response rate evaluation.
Participants in the Full Analysis Set who had lymphocytosis (ALC ≥ 4 × 10^9/L) at baseline and at least 1 evaluable postbaseline value were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	27	34	
Units: percentage of participants				
number (confidence interval 95%)	94.3 (87.2 to 98.1)	66.7 (46.0 to 83.5)	64.7 (46.5 to 80.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet Response Rate

End point title	Platelet Response Rate

End point description:

Platelet response rate was defined as the percentage of participants with baseline thrombocytopenia (platelet count < 100 x 10^9/L) who achieved an on-study platelet count ≥ 100 x 10^9/L or demonstrated a ≥ 50% increase in platelet count from baseline; platelet values within 4 weeks post-baseline or after 8 days post transfusion were excluded from the platelet response rate evaluation.
Participants in the Full Analysis Set who had thrombocytopenia (platelet count < 100 × 10^9/L) at baseline and at least 1 evaluable postbaseline value were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	23	10	
Units: percentage of participants				
number (confidence interval 95%)	98.0 (89.4 to 99.9)	73.9 (51.6 to 89.8)	100.0 (69.2 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin Response Rate

End point title	Hemoglobin Response Rate

End point description:

Hemoglobin response rate was defined as the percentage of participants with baseline anemia (hemoglobin < 110 g/L [11.0 g/dL]) who achieved an on-study hemoglobin ≥ 110 g/L (11.0 g/dL) or demonstrated a ≥ 50% increase in hemoglobin from baseline; hemoglobin values within 4 weeks post-baseline or after 4 weeks of receiving packed cell/whole blood transfusion or after 6 weeks of receiving exogenous growth factors (eg, darbepoetin alfa) were excluded from the hemoglobin response evaluation.
Participants in the Full Analysis Set who had anemia (hemoglobin < 110 g/L [11 g/dL]) at baseline and at least 1 evaluable postbaseline value were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	24	11	
Units: percentage of participants				
number (confidence interval 95%)	83.1 (71.0 to 91.6)	45.8 (25.6 to 67.2)	81.8 (48.2 to 97.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophil Response Rate

End point title	Neutrophil Response Rate

End point description:

Neutrophil response rate was defined as the percentage of participants with baseline neutropenia (absolute neutrophil count [ANC] ≤ 1.5 x 10^9/L) who achieved an ANC > 1.5 x 10^9/L or demonstrated a ≥ 50% increase in ANC from baseline; ANC values within 4 weeks of post-baseline or after 2 weeks of receiving exogenous growth factors (eg, filgrastim, granulocyte-colony stimulating factor [G-CSF], lenograstim) or after 4 weeks of receiving Neulasta® were excluded from response

evaluation.
Participants in the Full Analysis Set who had neutropenia (ANC ≤ 1.5 × 10^9/L) at baseline and at least 1 evaluable postbaseline value were analyzed.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	11	6	
Units: percentage of participants				
number (confidence interval 95%)	96.3 (81.0 to 99.9)	90.9 (58.7 to 99.8)	100.0 (54.1 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time interval from start of study therapy to death from any cause. Overall survival was analyzed using KM estimates. Data presented includes all available survival information from Study GS-US-312-0116 (including data in long-term follow-up) and Study GS-US-312-0117 (including any data in long-term follow-up) up to the database finalization dates. Data from surviving participants were censored at the last time that the participant was known to be alive on study or long-term follow-up. 999 = Too few events to estimate the upper limit of the confidence interval.
Per the analysis plan, overall survival data was analyzed in the ITT Analysis Set (participants who were randomized in the study) by treatment group according to the original randomization in Study GS-US-312-0116, regardless if participants received any study drug, or received a different regimen they were randomized to.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R	Placebo+R		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110	110		
Units: months				
median (confidence interval 95%)	40.6 (28.5 to 57.3)	34.6 (16.0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Change From Baseline in Health-Related Quality of Life (HRQL) Domain and Symptom Scores Based on the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) Questionnaire

End point title	Best Change From Baseline in Health-Related Quality of Life (HRQL) Domain and Symptom Scores Based on the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) Questionnaire

End point description:

The FACT-Leu questionnaire included subscales for physical well-being (PWB, 7 items), social/family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), functional well-being (FWB, 7 items), and additional concerns or Leukemia-Specific Subscale (LeuS, 17 items). The FACT-Leu scoring guide identified those negatively stated items that must have been reversed before being added to obtain subscale totals. Negatively stated items were reversed by subtracting the response from "4". After reversing proper items, all subscale items were summed to get total subscale scores with the range of 0-28, 0-28, 0-24, 0-28, 0-68 for PWB, SWB, EWB, FWB, and LeuS, respectively. FACT-Leu total score ranged from 0 to 176. Higher scores indicated a better quality of life. Best change from baseline was defined as the highest value of change from baseline among all postbaseline visits.
Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Study GS-US-312-0116 or GS-US-312-0117 Baseline up to Week 184

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	107	42	44	
Units: units on a scale				
arithmetic mean (standard deviation)				
Total Score: Baseline (n = 103, 42, 43)	128.4 (± 22.72)	116.7 (± 29.56)	128.1 (± 29.16)	
PWB: Baseline (n = 106, 42, 44)	22.8 (± 4.42)	20.2 (± 5.93)	21.9 (± 5.41)	
SWB: Baseline (n = 107, 42, 43)	22.5 (± 5.53)	22.5 (± 5.06)	23.5 (± 5.04)	
EWB: Baseline (n = 104, 42, 44)	19.1 (± 3.44)	17.3 (± 4.97)	17.6 (± 4.48)	
FWB: Baseline (n = 106, 42, 44)	18.0 (± 6.57)	15.0 (± 7.17)	18.0 (± 6.88)	
LeuS: Baseline (n = 106, 42, 44)	46.0 (± 10.64)	41.7 (± 12.74)	47.0 (± 12.01)	
Total Score:Best Change From Baseline(n=101,39,40)	21.8 (± 19.64)	20.2 (± 19.91)	14.9 (± 12.04)	
PWB: Best Change From Baseline (n = 102, 39, 40)	3.1 (± 4.65)	3.6 (± 4.26)	3.4 (± 3.81)	
SWB: Best Change From Baseline (n = 104, 39, 39)	2.9 (± 5.21)	2.0 (± 2.88)	2.1 (± 2.39)	
EWB: Best Change From Baseline (n = 101, 39, 40)	3.1 (± 2.75)	3.1 (± 3.68)	2.8 (± 3.14)	
FWB: Best Change From Baseline (n = 104, 39, 38)	5.1 (± 5.80)	4.1 (± 5.01)	3.1 (± 2.94)	
LueS: Best Change From Baseline (n = 104, 39, 41)	11.3 (± 9.13)	10.1 (± 8.78)	7.8 (± 5.59)	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Change From Baseline in Karnofsky Performance Status (KPS)

End point title	Best Change From Baseline in Karnofsky Performance Status (KPS)

End point description:

KPS is a tool used to measure the ability to perform ordinary tasks. The score ranges from 0 to 100, with a higher score indicating that the participant is better able to carry out daily activities. Best change from baseline was defined as the highest value of change from baseline among all postbaseline visits. For participants who did not enter Study
GS-US-312-0117, baseline values were from Study GS-US-312-0116.
Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Study GS-US-312-0116 or GS-US-312-0117 Baseline up to Week 190

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	42	44	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 110, 42, 44)	80.7 (± 12.47)	78.1 (± 14.18)	86.8 (± 8.83)	
Best Change (n = 105, 38, 35)	11.1 (± 10.31)	7.1 (± 8.67)	4.3 (± 6.98)	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Phosphatidylinositol 3-kinase (PI3Kδ)/Akt/Mammalian Target of Rapamycin (mTOR) Pathway Activation as a Measure of PI3Kδ Pathway Activity

End point title	Changes From Baseline in Phosphatidylinositol 3-kinase (PI3Kδ)/Akt/Mammalian Target of Rapamycin (mTOR) Pathway Activation as a Measure of PI3Kδ Pathway Activity

End point description:

Data were not collected because there was insufficient volume of sample (not enough material) to perform the analysis for any participant.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[3] - Data were not collected because there was insufficient volume of sample to perform the analysis.

[4] - Data were not collected because there was insufficient volume of sample to perform the analysis.

[5] - Data were not collected because there was insufficient volume of sample to perform the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Change From Baseline in the Plasma Concentrations of Disease-Associated Chemokines and Cytokines

End point title	Overall Change From Baseline in the Plasma Concentrations of Disease-Associated Chemokines and Cytokines

End point description:

To evaluate overall changes from the baseline of the longitudinal continuous biomarkers, the area under the curve (AUC) of biomarker changes from % baseline was calculated using the trapezoidal rule. The distribution of AUC for each biomarker was explored, and the median AUC for each biomarker were reported. The biomarkers with median AUC value of 100 indicated no overall on-treatment biomarker changes compared to the baseline.
The cytokine and T-cell subsets biomarker analysis set included all participants who received at least one dose of study drug, consented for optional future study, and had at least one evaluable measurement for any biomarker at any visit on IDL treatment. Available samples were batched for analysis as prespecified.

End point type	Secondary

End point timeframe:

GS-US-312-0116 Baseline to end of study GS-US-312-0117 (maximum: up to 67.6 months)

End point values	IDL/Placebo+R to IDL			
Subject group type	Subject analysis set			
Number of subjects analysed	174			
Units: AUC				
median (full range (min-max))				
Tumor Necrosis Factor (TNF)-alpha	36.73 (5.34 to 183.56)			
Macrophage Inflammatory Protein (MIP)1-alpha	26.55 (3.76 to 236.22)			
Interleukin (IL)-10	58.65 (2.36 to 1706.34)			
IL-15	111.18 (51.28 to 230.1)			
IL-12p40	64.89 (11.3 to 2012.31)			
RANTES (CCL5)	131.94 (6.76 to 3715.99)			
IL-1ra	114.22 (11.64 to 608.17)			

Interferon (IFN)-gamma	127.72 (10.55 to 4736.96)			
C-Reactive Protein (CRP)	132.38 (9.67 to 7625.53)			
IFN-gamma-induced protein (IP)-10 (CXCL10)	88.5 (15.24 to 786.21)			
IL-7	91.82 (14.47 to 960.7)			
Granulocyte-colony stimulating factor (G-CSF)	96.59 (3.83 to 1586.48)			
IL-17A	100 (8.8 to 1311.69)			
IL-6	100 (7.13 to 2817.44)			
IL-8	102.59 (2.47 to 1724.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Compliance as Assessed by the Percentage of Participants Adhering to Treatment

End point title	Study Drug Compliance as Assessed by the Percentage of Participants Adhering to Treatment

End point description:

Adherence percentage was calculated as the sum of tablets dispensed - the sum of tablets returned divided by the sum of the overall dosing period (total daily tablets x dosing duration), taking into account investigator-prescribed interruptions.
Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

First IDL dose date in study GS-US-312-0116 or GS-US-312-0117 to last IDL dose date in study GS-US-312-0117 (maximum: 67.3 months)

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	42	44	
Units: percentage of participants				
number (not applicable)				
Adherence ≥ 75%	100.0	97.6	100.0	
Adherence < 75%	0.0	2.4	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Trough (Predose) and Peak (1.5 Hours Postdose) Concentrations of Idelalisib

End point title	Plasma Trough (Predose) and Peak (1.5 Hours Postdose) Concentrations of Idelalisib[6]

End point description:

Participants in the pharmacokinetic (PK) Analysis Set (participants in the Full Analysis Set who had the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest) with available data were analyzed.

End point type	Secondary

End point timeframe:

Weeks 4, 12, and 24

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be carried out in the indicated arms.

End point values	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	IDL+R to IDL 150 mg	IDL+R (PD) to IDL 300 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	30	29	40	3
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
Week 4: Predose (n = 30, 29, 40, 3)	301.5 (195.0 to 494.0)	412.0 (211.0 to 646.0)	384.0 (166.5 to 681.5)	470.0 (317.0 to 631.0)
Week 4: 1.5 Hours Postdose (n = 29, 29, 38, 3)	2580.0 (1880.0 to 3080.0)	1720.0 (1200.0 to 2660.0)	2115.0 (1370.0 to 2750.0)	3940.0 (1550.0 to 4000.0)
Week 12: Predose (n = 29, 26, 35, 3)	335.0 (190.0 to 470.0)	298.0 (212.0 to 691.0)	370.0 (196.0 to 745.0)	570.0 (355.0 to 643.0)
Week 12: 1.5 Hours Postdose (n = 28, 26, 32, 3)	2245.0 (1655.0 to 3255.0)	1940.0 (1430.0 to 2450.0)	2110.0 (1595.0 to 2665.0)	3800.0 (3160.0 to 4710.0)
Week 24: Predose (n = 19, 16, 33, 3)	362.0 (162.0 to 550.0)	350.5 (261.0 to 504.5)	307.0 (179.0 to 584.0)	637.0 (524.0 to 930.0)
Week 24: 1.5 Hours Postdose (n = 19, 17, 34, 3)	2180.0 (1760.0 to 2980.0)	2010.0 (1210.0 to 2430.0)	2270.0 (1560.0 to 2790.0)	5630.0 (5550.0 to 5660.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Health Status as Assessed Using the EuroQoL Five-Dimension (EQ-5D) Utility Measure

End point title	Change in Health Status as Assessed Using the EuroQoL Five-Dimension (EQ-5D) Utility Measure

End point description:

Change in health status was defined as the change from baseline in overall health and single-item dimension scores as assessed using the EQ-5D utility measure. Percentage of participants with different level of problem were reported. Level 1: indicated no problem; Level 2: indicated some problems; and Level 3: indicated extreme problems. For
participants who did not enter Study GS-US-312-0117, baseline values were from Study GS-US-312-0116. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:
Study GS-US-312-0116 or GS-US-312-0117 Baseline; Weeks 24 and 48

End point values	IDL+R to IDL	Placebo+R (PD) to IDL 150 mg	Placebo+R to IDL 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	42	44	
Units: percentage of participants				
number (not applicable)				
Baseline: Anxiety/Depression, Level 1(n=108,42,44)	70.4	50.0	56.8	
Baseline: Anxiety/Depression, Level 2(n=108,42,44)	28.7	42.9	43.2	
Baseline: Anxiety/Depression, Level 3(n=108,42,44)	0.9	7.1	0.0	
Baseline: Mobility, Level 1 (n=108,42,44)	60.2	38.1	61.4	
Baseline: Mobility, Level 2 (n=108,42,44)	39.8	59.5	38.6	
Baseline: Mobility, Level 3 (n=108,42,44)	0.0	2.4	0.0	
Baseline: Pain/Discomfort, Level 1 (n=108,42,44)	53.3	50.0	45.5	
Baseline: Pain/Discomfort, Level 2 (n=108,42,44)	39.3	45.2	50.0	
Baseline: Pain/Discomfort, Level 3 (n=108,42,44)	7.5	4.8	4.5	
Baseline: Self-Care, Level 1 (n=108,42,44)	90.7	76.2	84.1	
Baseline: Self-Care, Level 2 (n=108,42,44)	9.3	19.0	15.9	
Baseline: Self-Care, Level 3 (n=108,42,44)	0.0	4.8	0.0	
Baseline: Usual Activities, Level 1 (n=108,42,44)	56.5	28.6	52.3	
Baseline: Usual Activities, Level 2 (n=108,42,44)	36.1	52.4	45.5	
Baseline: Usual Activities, Level 3 (n=108,42,44)	7.4	19.0	2.3	
Week 24: Anxiety/Depression, Level 1 (n=77,20,23)	83.1	65.0	69.6	
Week 24: Anxiety/Depression, Level 2 (n=77,20,23)	15.6	35.0	30.4	
Week 24: Anxiety/Depression, Level 3 (n=77,20,23)	1.3	0.0	0.0	
Week 24: Mobility, Level 1 (n=77,20,23)	70.1	65.0	69.6	
Week 24: Mobility, Level 2 (n=77,20,23)	29.9	35.0	30.4	
Week 24: Mobility, Level 3 (n=77,20,23)	0.0	0.0	0.0	
Week 24: Pain/Discomfort, Level 1 (n=77,20,23)	62.3	65.0	43.5	
Week 24: Pain/Discomfort, Level 2 (n=77,20,23)	35.1	30.0	47.8	

Week 24: Pain/Discomfort, Level 3 (n=77,20,23)	2.6	5.0	8.7	
Week 24: Self-Care, Level 1 (n=77,20,23)	92.2	85.0	91.3	
Week 24: Self-Care, Level 2 (n=77,20,23)	6.5	15.0	8.7	
Week 24: Self-Care, Level 3 (n=77,20,23)	1.3	0.0	0.0	
Week 24: Usual Activities, Level 1 (n=77,20,23)	68.4	75.0	60.9	
Week 24: Usual Activities, Level 2 (n=77,20,23)	28.9	25.0	34.8	
Week 24: Usual Activities, Level 3 (n=77,20,23)	2.6	0.0	4.3	
Week 48: Anxiety/Depression, Level 1 (n=44,10,6)	84.1	90.0	50.0	
Week 48: Anxiety/Depression, Level 2 (n=44,10,6)	15.9	10.0	50.0	
Week 48: Anxiety/Depression, Level 3 (n=44,10,6)	0.0	0.0	0.0	
Week 48: Mobility, Level 1 (n=44,10,6)	72.7	60.0	66.7	
Week 48: Mobility, Level 2 (n=44,10,6)	27.3	40.0	33.3	
Week 48: Mobility, Level 3 (n=44,10,6)	0.0	0.0	0.0	
Week 48: Pain/Discomfort, Level 1 (n=44,10,6)	56.8	60.0	50.0	
Week 48: Pain/Discomfort, Level 2 (n=44,10,6)	43.2	30.0	50.0	
Week 48: Pain/Discomfort, Level 3 (n=44,10,6)	0.0	10.0	0.0	
Week 48: Self-Care, Level 1 (n=44,10,6)	95.5	90.0	83.3	
Week 48: Self-Care, Level 2 (n=44,10,6)	4.5	0.0	16.7	
Week 48: Self-Care, Level 3 (n=44,10,6)	0.0	10.0	0.0	
Week 48: Usual Activities, Level 1 (n=44,10,6)	72.7	70.0	50.0	
Week 48: Usual Activities, Level 2 (n=44,10,6)	25.0	20.0	33.3	
Week 48: Usual Activities, Level 3 (n=44,10,6)	2.3	10.0	16.7	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: First IDL dose date in study GS-US-312-0116 or GS-US-312-0117 to last IDL dose date in study GS-US-312-0117 (maximum: 67.3 months) plus 30 days;
All-Cause Mortality: First IDL dose date up to 67.6 months

Adverse event reporting additional description:

Only adverse events occurring in participants who enrolled into the extension Study GS-US-312-0117 were included. Adverse events occurring in the parent study, GS-US-312-0116, are reported in EudraCT record 2011-005180-24.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	IDL+R to IDL 150 mg

Reporting group description:

Adverse events reported in this group occurred during the extension Study GS-US-312-0117 in participants who received IDL 150 mg tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group title	IDL+R (PD) to IDL 300 mg

Reporting group description:

Adverse events reported in this group occurred during the extension Study GS-US-312-0117 in participants who received IDL 150 mg tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 300 mg tablet twice daily.

Reporting group title	Placebo+R (PD) to IDL 150 mg

Reporting group description:

Adverse events reported in this group occurred during the extension Study GS-US-312-0117 in participants who received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and met the primary endpoint of PD and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Reporting group title	Placebo+R to IDL 150 mg

Reporting group description:

Adverse events reported in this group occurred during the extension Study GS-US-312-0117 in participants who received placebo tablet twice daily plus rituximab (8 infusions intravenously) in Study GS-US-312-0116 and entered Study GS-US-312-0117 to receive IDL 150 mg tablet twice daily.

Serious adverse events	IDL+R to IDL 150 mg	IDL+R (PD) to IDL 300 mg	Placebo+R (PD) to IDL 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 71 (76.06%)	2 / 4 (50.00%)	34 / 42 (80.95%)
number of deaths (all causes)	37	3	25
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			

subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder papilloma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kaposi's sarcoma			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung squamous cell carcinoma metastatic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melanoma recurrent			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal syndrome			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pneumonitis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 2
Pleural effusion			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Weight decreased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Splenic rupture			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Acute myocardial infarction			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Central nervous system haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	5 / 42 (11.90%)
occurrences causally related to treatment / all	1 / 4	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thrombocytopenia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences causally related to treatment / all	6 / 8	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Colitis			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	6 / 6	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pruritic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 71 (8.45%)	2 / 4 (50.00%)	10 / 42 (23.81%)
occurrences causally related to treatment / all	0 / 7	0 / 2	3 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 3
Cellulitis			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Neutropenic sepsis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abscess limb			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral fungal infection			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal infection			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia escherichia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumonia pneumococcal			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis pasteurella			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis fungal			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenotrophomonas infection			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeding intolerance			

subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo+R to IDL 150 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 44 (72.73%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Anal squamous cell carcinoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder papilloma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder transitional cell carcinoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraductal proliferative breast lesion				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Kaposi's sarcoma				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung squamous cell carcinoma metastatic				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melanoma recurrent				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myelodysplastic syndrome				

subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neuroendocrine carcinoma of the skin				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal carcinoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic aneurysm				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic dissection				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	4 / 44 (9.09%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				

subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Drug withdrawal syndrome				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				

subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchiectasis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				

subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Hip fracture				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Fall			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Atrial fibrillation				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Haemorrhage intracranial				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Central nervous system				

haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Vitreous haemorrhage				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	8 / 44 (18.18%)			
occurrences causally related to treatment / all	7 / 9			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis haemorrhagic				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema multiforme				

subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash pruritic				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polymyalgia rheumatica				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Cellulitis			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonal bacteraemia			

subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Abscess limb				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute sinusitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral fungal infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Furuncle				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of bronchiectasis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia escherichia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia haemophilus				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia influenzal				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia respiratory syncytial viral				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Progressive multifocal leukoencephalopathy				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis pasteurella				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis fungal				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stenotrophomonas infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypercalcaemia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Feeding intolerance				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour lysis syndrome				

subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	IDL+R to IDL 150 mg	IDL+R (PD) to IDL 300 mg	Placebo+R (PD) to IDL 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 71 (98.59%)	4 / 4 (100.00%)	41 / 42 (97.62%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	7	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	4	0	2
Hypertension			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	4	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 71 (23.94%)	0 / 4 (0.00%)	12 / 42 (28.57%)
occurrences (all)	23	0	14
Fatigue			
subjects affected / exposed	15 / 71 (21.13%)	2 / 4 (50.00%)	13 / 42 (30.95%)
occurrences (all)	16	2	13
Oedema peripheral			
subjects affected / exposed	12 / 71 (16.90%)	0 / 4 (0.00%)	7 / 42 (16.67%)
occurrences (all)	12	0	7
Chills			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	6 / 42 (14.29%)
occurrences (all)	8	0	6
Asthenia			

subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	7 / 42 (16.67%)
occurrences (all)	5	0	7
Pain			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	3	0	3
Malaise			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	2
Mucosal inflammation			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Peripheral swelling			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Oedema			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	3	0	2
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	4	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 71 (29.58%)	0 / 4 (0.00%)	12 / 42 (28.57%)
occurrences (all)	22	0	19
Dyspnoea			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	8	0	4
Productive cough			

subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	9	0	0
Epistaxis			
subjects affected / exposed	2 / 71 (2.82%)	1 / 4 (25.00%)	3 / 42 (7.14%)
occurrences (all)	2	1	5
Lung infiltration			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	5	0	3
Pleural effusion			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	2	0	4
Dyspnoea exertional			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	5	0	1
Oropharyngeal pain			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	4	0	1
Pneumonitis			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	3	0	1
Nasal congestion			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	5	0	1
Sinus congestion			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	4	0	6
Hypoxia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Pulmonary congestion			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Nasal ulcer			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	6	0	3
Anxiety			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	2	0	3
Depression			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	3	0	0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Investigations			
Weight decreased			
subjects affected / exposed	5 / 71 (7.04%)	1 / 4 (25.00%)	4 / 42 (9.52%)
occurrences (all)	5	1	4
Alanine aminotransferase increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Computerised tomogram thorax abnormal			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	3	0	0
Contusion			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	1	0	3
Laceration			

subjects affected / exposed	3 / 71 (4.23%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	3	1	0
Humerus fracture			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Joint injury			
subjects affected / exposed	1 / 71 (1.41%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	6	0	3
Dizziness			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	5 / 42 (11.90%)
occurrences (all)	3	0	5
Lethargy			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	6	0	4
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 71 (19.72%)	1 / 4 (25.00%)	9 / 42 (21.43%)
occurrences (all)	20	3	17
Anaemia			
subjects affected / exposed	8 / 71 (11.27%)	2 / 4 (50.00%)	5 / 42 (11.90%)
occurrences (all)	8	2	7
Thrombocytopenia			
subjects affected / exposed	5 / 71 (7.04%)	2 / 4 (50.00%)	3 / 42 (7.14%)
occurrences (all)	6	2	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	30 / 71 (42.25%)	2 / 4 (50.00%)	17 / 42 (40.48%)
occurrences (all)	48	8	33
Nausea			

subjects affected / exposed	11 / 71 (15.49%)	0 / 4 (0.00%)	12 / 42 (28.57%)
occurrences (all)	13	0	13
Constipation			
subjects affected / exposed	11 / 71 (15.49%)	1 / 4 (25.00%)	7 / 42 (16.67%)
occurrences (all)	12	1	7
Vomiting			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	7 / 42 (16.67%)
occurrences (all)	12	0	9
Abdominal pain			
subjects affected / exposed	8 / 71 (11.27%)	1 / 4 (25.00%)	5 / 42 (11.90%)
occurrences (all)	10	1	5
Haemorrhoids			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	2	0	4
Colitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	1	0	4
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 71 (2.82%)	1 / 4 (25.00%)	5 / 42 (11.90%)
occurrences (all)	2	1	5
Dyspepsia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	4	0	2
Flatulence			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Abdominal distension			
subjects affected / exposed	3 / 71 (4.23%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	3	1	0
Stomatitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dysphagia			

subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	2 / 42 (4.76%)
occurrences (all)	0	1	2
Oesophageal ulcer			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	6 / 71 (8.45%)	1 / 4 (25.00%)	10 / 42 (23.81%)
occurrences (all)	6	1	11
Rash			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	6	0	4
Rash maculo-papular			
subjects affected / exposed	5 / 71 (7.04%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	6	0	2
Skin lesion			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	3	0	2
Pruritus			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Dry skin			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 71 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	7	0	1
Haematuria			
subjects affected / exposed	5 / 71 (7.04%)	1 / 4 (25.00%)	1 / 42 (2.38%)
occurrences (all)	5	1	1
Dysuria			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 71 (8.45%)	1 / 4 (25.00%)	5 / 42 (11.90%)
occurrences (all)	6	1	5
Pain in extremity			
subjects affected / exposed	8 / 71 (11.27%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	8	0	2
Arthralgia			
subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	7	0	0
Myalgia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 71 (14.08%)	0 / 4 (0.00%)	8 / 42 (19.05%)
occurrences (all)	14	0	9
Sinusitis			
subjects affected / exposed	14 / 71 (19.72%)	1 / 4 (25.00%)	1 / 42 (2.38%)
occurrences (all)	16	1	1
Pneumonia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	9 / 42 (21.43%)
occurrences (all)	4	0	9
Bronchitis			
subjects affected / exposed	4 / 71 (5.63%)	1 / 4 (25.00%)	2 / 42 (4.76%)
occurrences (all)	4	2	2

Urinary tract infection			
subjects affected / exposed	7 / 71 (9.86%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	9	0	3
Lower respiratory tract infection			
subjects affected / exposed	3 / 71 (4.23%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	5	0	1
Herpes zoster			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	2
Nasopharyngitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	2	0	1
Cellulitis			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	5	0	0
Pharyngitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	2	0	1
Ear infection			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	5	0	1
Oral candidiasis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	8 / 71 (11.27%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	10	0	3
Decreased appetite			
subjects affected / exposed	9 / 71 (12.68%)	1 / 4 (25.00%)	1 / 42 (2.38%)
occurrences (all)	10	1	1
Hypomagnesaemia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	4	0	3
Dehydration			

subjects affected / exposed	6 / 71 (8.45%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	6	0	1
Hyponatraemia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Gout			
subjects affected / exposed	0 / 71 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4

Non-serious adverse events	Placebo+R to IDL 150 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 44 (36.36%)		
occurrences (all)	25		
Fatigue			
subjects affected / exposed	9 / 44 (20.45%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	5		

Asthenia subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 3		
Pain subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 5		
Malaise subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Mucosal inflammation subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Peripheral swelling subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 4		
Oedema subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Immune system disorders Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		
Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	16 / 44 (36.36%) 21		
Dyspnoea subjects affected / exposed occurrences (all)	10 / 44 (22.73%) 10		

Productive cough				
subjects affected / exposed	7 / 44 (15.91%)			
occurrences (all)	8			
Epistaxis				
subjects affected / exposed	4 / 44 (9.09%)			
occurrences (all)	4			
Lung infiltration				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Pleural effusion				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Dyspnoea exertional				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Oropharyngeal pain				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Pneumonitis				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Nasal congestion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Sinus congestion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Hypoxia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Pulmonary congestion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Nasal ulcer				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			

Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Product issues			
Device occlusion			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Investigations			
Weight decreased			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Computerised tomogram thorax abnormal			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Contusion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	2		
Laceration			

subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Humerus fracture subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		
Joint injury subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		
Post procedural haemorrhage subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 9		
Dizziness subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 8		
Lethargy subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 8		
Anaemia subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	26 / 44 (59.09%) 47		
Nausea			

subjects affected / exposed	12 / 44 (27.27%)			
occurrences (all)	16			
Constipation				
subjects affected / exposed	4 / 44 (9.09%)			
occurrences (all)	4			
Vomiting				
subjects affected / exposed	9 / 44 (20.45%)			
occurrences (all)	12			
Abdominal pain				
subjects affected / exposed	5 / 44 (11.36%)			
occurrences (all)	5			
Haemorrhoids				
subjects affected / exposed	6 / 44 (13.64%)			
occurrences (all)	6			
Colitis				
subjects affected / exposed	6 / 44 (13.64%)			
occurrences (all)	6			
Gastrooesophageal reflux disease				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	3			
Flatulence				
subjects affected / exposed	4 / 44 (9.09%)			
occurrences (all)	4			
Abdominal distension				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Dry mouth				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Dysphagia				

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Oesophageal ulcer			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	8		
Rash maculo-papular			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Skin lesion			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Rash macular			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Dermatitis acneiform			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	13		
Sinusitis			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	7		
Bronchitis			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	8		

Urinary tract infection subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 2		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 6		
Herpes zoster subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 7		
Cellulitis subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Pharyngitis subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Ear infection subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	7 / 44 (15.91%) 10		
Decreased appetite subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Hypomagnesaemia subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Dehydration			

subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Gout			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2013	The following changes were made: - Updated information regarding endpoints - Clarified that the independent review committee (IRC) findings will be considered primary for analyses of PFS and other tumor control endpoints - Updated risk section to include phototoxicity risk - Added urine pregnancy testing every 4 weeks and every visit after Visit 11 - Updated inclusion criteria relating to contraception
10 September 2013	The following changes were made: - To accommodate stopping the study early should the primary study be stopped early due to overwhelming efficacy, the following items have been revised: -- Study schema modified to accommodate an open-label portion following unblinding -- Description of the treatment groups and treatment assignments to indicate that participants who enroll post unblinding of the primary study will receive IDL at 150 mg twice daily -- Inclusion/exclusion criteria modified to include specific criteria for participants who are participating in the primary study at the time it is unblinded -- Statistical considerations modified to clarify that primary analysis will occur following unblinding - Updated disease response criteria to align with revised IRC Charter - Modified text in protocol Section 5.6.7, Drugs that Alter cytochrome P450 enzyme (CYP) 3A (CYP3A)-Dependent Metabolism and text throughout regarding CYP3A inhibitors or inducers to reflect current PK and pharmacodynamic research on IDL and its major metabolite, GS-563117 - Updated the nonclinical pharmacology and metabolism, nonclinical toxicology, clinical pharmacology, and PK sections to align with current analysis and to simplify and remove redundancy with the investigator's brochure (IB) - Updated data for the recently completed Phase 1 monotherapy study in participants with hematologic malignancies - Deleted protocol Table 6-17 as blood volumes are provided in the laboratory manual - Added significant participant noncompliance and initiation of another anticancer therapy as a reason for study withdrawal - Added protocol Section 6.3 to allow biological samples collected as a study procedure or as standard of care to be stored for future research (with participant's informed consent) to investigate the safety and mechanism of action of the study drug and the effects of treatment on the disease
16 December 2013	The following changes were made: - Updated toxicology to reflect current understanding of the effect of IDL - Following unblinding of the study, replaced standard-of-care follow-up imaging for participants randomized to IDL on Study GS-US-312-0116 with central review and made imaging time points consistent with collection prior to unblinding - Specified which data were collected during long-term follow-up
27 May 2014	The following changes were made: - The schedule of study visits was changed to every 12 weeks for participants who were randomized to IDL in Study GS-US-312-0116 so that participants did not have to come in more frequently in Study GS-US-312-0117. - Participants who were randomized to placebo in Study GS-US-312-0116 had study visits every 12 weeks once they have received IDL for 24 weeks cumulative across both studies. - Updates were made to describe the analysis performed for the blinded portion of the study as well as the analysis to be performed for the unblinded portion of the study, as the protocol did not previously differentiate these analyses.

10 October 2014	The following changes were made: - To update the general information on IDL to reflect approval status in the US and European Union - To align the following information with IB Edition 11: -- Guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events -- Information regarding the interaction of IDL with CYP3A enzyme inhibitors, inducers, and substrates - Based on recommendation from the Gilead Clinical Pharmacology Department, the 1.5-hour postdose IDL PK sample collection window was revised to ± 15 minutes
28 March 2016	The following changes were made: - The IDL safety information and guidelines for toxicity management were updated to be consistent across IDL protocols. - Increased monitoring for serious infections was added, including: -- Mandated prophylactic therapy for Pneumocystis jirovecii pneumonia (PJP) -- Cytomegalovirus (CMV) surveillance
05 August 2016	The following changes were made: - Adverse event monitoring and response procedures were revised for alignment with urgent safety measures. - Clarifications were added about recommended versus required actions related to adverse events, including: -- Required dose modifications and dose interruptions following occurrence of adverse events were added. -- Required weekly monitoring of ANC for neutropenia was added. -- The duration of required PJP prophylactic therapy was clarified. -- Required discontinuation of study drug was added for the following participants: those diagnosed with any grade of Stevens-Johnson syndrome or toxic epidermal necrolysis, Grade ≥ 2 pneumonitis, or PJP, and those whose benefit-risk profile was not deemed positive by the investigator.
24 October 2016	In order to provide clear guidance for IDL administration in the event of pneumonitis, the language around actions to be taken was revised.
21 September 2017	The following changes were made: - As the primary endpoint of the parent study (GS-US-312-0116) had been met, the schedule of required computed tomography (CT) scans was modified in order to decrease radiation exposure to participants and administrative burden to both participants and investigative sites. The protocol requested one final scan at disease progression or discontinuation. - Recommendations regarding IDL dose modifications for particular adverse events were required in order to align with the summary of product characteristics (SmPC) guidance. - Organizing pneumonia (OP) emerged as a potential safety signal during Gilead routine signal detection monitoring. This risk was included in the IB. All protocols with ongoing participants were being amended to add OP as a potential risk.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30995176