Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS 1101) in Combination with Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas

Summary

EudraCT number	2012-004034-42
Trial protocol	DE GB SE ES CZ IT
Global end of trial date	17 May 2016

Results information

Result version number	v2 (current)
This version publication date	18 May 2019
First version publication date	15 April 2017
Version creation reason	• Correction of full data set Adding text to "Limitations and Caveats" section

Trial information

Trial identification

Sponsor protocol code	GS-US-313-0125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01732926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	Gilead Sciences, Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@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	17 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the addition of idelalisib to bendamustine/rituximab on progression-free survival (PFS) in adults with previously treated indolent non-Hodgkin lymphoma (iNHL).

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	02 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 66
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 53
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Australia: 67
Country: Number of subjects enrolled	Germany: 3

Country: Number of subjects enrolled	Italy: 35
Worldwide total number of subjects	475
EEA total number of subjects	237

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	264
From 65 to 84 years	208
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the North America, Europe, and Asia Pacific. The first participant was screened on 02 January 2013. The last study visit occurred on 17 May 2016.

Pre-assignment

Screening details:

581 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Idelalisib + Bendamustine + Rituximab

Arm description:

Idelalisib (Zydelig®) 150 mg tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)

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

Dosage and administration details:

150 mg administered twice daily

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	Treanda®, Levact®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered starting at a dose of 90 mg/m^2 for up to 12 infusions

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan®, MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single use vials administered at a dose of 375 mg/m^2 starting on Day 1 for a total of 6 infusions

Arm title	Placebo + Bendamustine + Rituximab

Arm description:

Placebo tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
Administered twice daily

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	Treanda® , Levact®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Administered starting at a dose of 90 mg/m^2 for up to 12 infusions

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan®, MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Single use vials administered at a dose of 375 mg/m^2 starting on Day 1 for a total of 6 infusions

Number of subjects in period 1	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab
Started	320	155
Completed	53	45
Not completed	267	110
Blind Intentionally Broken by Subject/Study Site	1	1
Physician decision	24	11
Initiation of Other Anti-Cancer Therapy	7	6
Other Reason	21	4
Withdrawal by Subject	46	8
Study Terminated by Sponsor	168	80

Baseline characteristics

Reporting groups	
Reporting group title	Idelalisib + Bendamustine + Rituximab
Reporting group description:	
Idelalisib (Zydelig®) 150 mg tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)	
Reporting group title	Placebo + Bendamustine + Rituximab
Reporting group description:	
Placebo tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)	

Reporting group values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab	Total
Number of subjects	320	155	475
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62	62	
standard deviation	± 10.5	± 11.7	-
Gender categorical Units: Subjects			
Female	132	58	190
Male	188	97	285
Race Units: Subjects			
Asian	26	8	34
Black or African American	2	2	4
White	247	122	369
Other	4	2	6
Not Permitted	41	21	62
Ethnicity Units: Subjects			
Hispanic or Latino	16	8	24
Not Hispanic or Latino	262	129	391
Not Permitted	42	18	60

End points

End points reporting groups

Reporting group title	Idelalisib + Bendamustine + Rituximab

Reporting group description:

Idelalisib (Zydelig®) 150 mg tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)

Reporting group title	Placebo + Bendamustine + Rituximab

Reporting group description:

Placebo tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)

Primary: Progression-free Survival (PFS)

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

End point description:

PFS is defined as the interval from randomization to the earlier of the first documentation of definitive indolent non-Hodgkin lymphomas (iNHL) disease progression or death from any cause. Definitive iNHL disease progression is progression based on standard criteria. PFS was to be assessed by an independent review committee (IRC). Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Primary

End point timeframe:

Not applicable

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: Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Not apllicable				

Notes:

[2] - Analysis was not performed due to early study termination.

[3] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate (CR)

End point title	Complete Response Rate (CR)

End point description:

Complete response rate is defined as the proportion of participants who achieve a complete response. CR rate was to be assessed by an IRC.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Not applicable				

Notes:

[4] - Analysis was not performed due to early study termination.

[5] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall response rate is defined as the proportion of participants who achieve a complete response or partial response (or very good partial response (VGPR) or minor response (MR) for participants with Waldenstrom's). ORR was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Not applicable				

Notes:

[6] - Analysis was not performed due to early study termination

[7] - Analysis was not performed due to early study termination

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 is defined as the proportion of participants who achieve ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions. Lymph node response rate was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Not applicable				

Notes:

[8] - Analysis was not performed due to early study termination.

[9] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the interval from randomization to death from any cause. Due to the early termination of the study, efficacy data were not mature for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Not applicable				

Notes:

[10] - Analysis was not performed due to early study termination.

[11] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 34 months plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: all participants who took at least 1 dose of study drug

NOTE: Serious adverse events and deaths causally related to "treatment" refers to events deemed related to idelalisib treatment per investigator assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo + Bendamustine + Rituximab

Reporting group description:

Placebo tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab interavenously (375 mg/m^2 on Day 1 for a total of 6 infusions)

Reporting group title	Idelalisib + Bendamustine + Rituximab

Reporting group description:

Idelalisib 150 mg tablet twice daily + bendamustine intravenously (starting dose of 90 mg/m^2 for up to 12 infusions) + rituximab intravenously (375 mg/m^2 on Day 1 for a total of 6 infusions)

Serious adverse events	Placebo + Bendamustine + Rituximab	Idelalisib + Bendamustine + Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 155 (37.42%)	229 / 317 (72.24%)	
number of deaths (all causes)	13	31	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 155 (0.65%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal carcinoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Richter's syndrome			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 155 (0.65%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 155 (0.65%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypovolaemic shock			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related thrombosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 155 (1.29%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 155 (1.29%)	67 / 317 (21.14%)	
occurrences causally related to treatment / all	1 / 2	37 / 96	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 155 (0.65%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 155 (0.00%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Aspiration			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hydrothorax			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 155 (0.65%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 155 (0.00%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 155 (0.00%)	16 / 317 (5.05%)	
occurrences causally related to treatment / all	0 / 0	15 / 17	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 155 (0.00%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 4	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 155 (0.00%)	14 / 317 (4.42%)	
occurrences causally related to treatment / all	0 / 0	13 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 155 (0.00%)	12 / 317 (3.79%)	
occurrences causally related to treatment / all	0 / 0	11 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	3 / 155 (1.94%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 155 (1.94%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sacroiliac fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilatation ventricular			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex regional pain syndrome			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed dementia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 155 (2.58%)	8 / 317 (2.52%)	
occurrences causally related to treatment / all	1 / 4	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia pure red cell			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 155 (4.52%)	45 / 317 (14.20%)	
occurrences causally related to treatment / all	2 / 8	34 / 60	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemolytic anaemia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 155 (1.94%)	8 / 317 (2.52%)	
occurrences causally related to treatment / all	4 / 4	7 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 155 (1.29%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ophthalmoplegia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 155 (0.00%)	9 / 317 (2.84%)	
occurrences causally related to treatment / all	0 / 0	9 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 155 (1.29%)	14 / 317 (4.42%)	
occurrences causally related to treatment / all	1 / 2	14 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 155 (0.65%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	0 / 1	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 155 (0.65%)	8 / 317 (2.52%)	
occurrences causally related to treatment / all	0 / 1	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecchymosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised erythema			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pustular psoriasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 155 (0.00%)	18 / 317 (5.68%)	
occurrences causally related to treatment / all	0 / 0	13 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 155 (0.00%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 155 (0.00%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 155 (1.29%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	1 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			

subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 155 (0.65%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 155 (0.00%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	0 / 0	7 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enteritis infectious			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 155 (1.29%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 155 (0.65%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 155 (0.65%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 155 (1.94%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	2 / 3	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenic sepsis			
subjects affected / exposed	2 / 155 (1.29%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	2 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 155 (0.65%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 155 (0.00%)	9 / 317 (2.84%)	
occurrences causally related to treatment / all	0 / 0	6 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			

subjects affected / exposed	4 / 155 (2.58%)	24 / 317 (7.57%)	
occurrences causally related to treatment / all	0 / 4	12 / 25	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pneumonia bacterial			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	2 / 155 (1.29%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 155 (0.65%)	9 / 317 (2.84%)	
occurrences causally related to treatment / all	0 / 1	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	2 / 155 (1.29%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	2 / 2	
Sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mycosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 155 (0.00%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 155 (0.65%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 155 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	1 / 155 (0.65%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 155 (0.65%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	1 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 155 (0.00%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Bendamustine + Rituximab	Idelalisib + Bendamustine + Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 155 (94.84%)	315 / 317 (99.37%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 155 (3.23%)	16 / 317 (5.05%)	
occurrences (all)	5	18	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 155 (15.48%)	43 / 317 (13.56%)	
occurrences (all)	27	55	
Chills			
subjects affected / exposed	10 / 155 (6.45%)	39 / 317 (12.30%)	
occurrences (all)	13	45	
Fatigue			

subjects affected / exposed	51 / 155 (32.90%)	103 / 317 (32.49%)	
occurrences (all)	57	125	
Mucosal inflammation			
subjects affected / exposed	2 / 155 (1.29%)	29 / 317 (9.15%)	
occurrences (all)	2	35	
Oedema peripheral			
subjects affected / exposed	7 / 155 (4.52%)	38 / 317 (11.99%)	
occurrences (all)	7	45	
Pyrexia			
subjects affected / exposed	22 / 155 (14.19%)	135 / 317 (42.59%)	
occurrences (all)	39	217	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 155 (23.87%)	71 / 317 (22.40%)	
occurrences (all)	40	93	
Dyspnoea			
subjects affected / exposed	11 / 155 (7.10%)	40 / 317 (12.62%)	
occurrences (all)	12	48	
Oropharyngeal pain			
subjects affected / exposed	10 / 155 (6.45%)	25 / 317 (7.89%)	
occurrences (all)	11	33	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 155 (10.32%)	40 / 317 (12.62%)	
occurrences (all)	16	47	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 155 (1.94%)	65 / 317 (20.50%)	
occurrences (all)	5	87	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 155 (2.58%)	51 / 317 (16.09%)	
occurrences (all)	5	69	
Neutrophil count decreased			
subjects affected / exposed	9 / 155 (5.81%)	12 / 317 (3.79%)	
occurrences (all)	15	15	
Weight decreased			

subjects affected / exposed	6 / 155 (3.87%)	41 / 317 (12.93%)	
occurrences (all)	6	44	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	16 / 155 (10.32%)	38 / 317 (11.99%)	
occurrences (all)	28	51	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 155 (6.45%)	23 / 317 (7.26%)	
occurrences (all)	10	26	
Dysgeusia			
subjects affected / exposed	10 / 155 (6.45%)	16 / 317 (5.05%)	
occurrences (all)	22	16	
Headache			
subjects affected / exposed	18 / 155 (11.61%)	45 / 317 (14.20%)	
occurrences (all)	21	61	
Neuropathy peripheral			
subjects affected / exposed	9 / 155 (5.81%)	8 / 317 (2.52%)	
occurrences (all)	9	8	
Paraesthesia			
subjects affected / exposed	9 / 155 (5.81%)	9 / 317 (2.84%)	
occurrences (all)	9	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 155 (11.61%)	51 / 317 (16.09%)	
occurrences (all)	25	72	
Leukopenia			
subjects affected / exposed	7 / 155 (4.52%)	18 / 317 (5.68%)	
occurrences (all)	12	23	
Neutropenia			
subjects affected / exposed	54 / 155 (34.84%)	122 / 317 (38.49%)	
occurrences (all)	102	262	
Thrombocytopenia			
subjects affected / exposed	18 / 155 (11.61%)	37 / 317 (11.67%)	
occurrences (all)	26	48	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	11 / 155 (7.10%)	39 / 317 (12.30%)	
occurrences (all)	13	47	
Abdominal pain upper			
subjects affected / exposed	10 / 155 (6.45%)	21 / 317 (6.62%)	
occurrences (all)	10	25	
Constipation			
subjects affected / exposed	31 / 155 (20.00%)	74 / 317 (23.34%)	
occurrences (all)	34	88	
Diarrhoea			
subjects affected / exposed	33 / 155 (21.29%)	158 / 317 (49.84%)	
occurrences (all)	44	260	
Dry mouth			
subjects affected / exposed	3 / 155 (1.94%)	20 / 317 (6.31%)	
occurrences (all)	3	21	
Dyspepsia			
subjects affected / exposed	9 / 155 (5.81%)	28 / 317 (8.83%)	
occurrences (all)	15	33	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 155 (3.87%)	17 / 317 (5.36%)	
occurrences (all)	6	18	
Mouth ulceration			
subjects affected / exposed	4 / 155 (2.58%)	20 / 317 (6.31%)	
occurrences (all)	5	21	
Nausea			
subjects affected / exposed	65 / 155 (41.94%)	159 / 317 (50.16%)	
occurrences (all)	106	236	
Stomatitis			
subjects affected / exposed	5 / 155 (3.23%)	26 / 317 (8.20%)	
occurrences (all)	5	27	
Vomiting			
subjects affected / exposed	25 / 155 (16.13%)	100 / 317 (31.55%)	
occurrences (all)	44	144	
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed	5 / 155 (3.23%)	20 / 317 (6.31%)	
occurrences (all)	5	20	
Erythema			
subjects affected / exposed	4 / 155 (2.58%)	20 / 317 (6.31%)	
occurrences (all)	5	28	
Night sweats			
subjects affected / exposed	6 / 155 (3.87%)	16 / 317 (5.05%)	
occurrences (all)	6	17	
Pruritus			
subjects affected / exposed	22 / 155 (14.19%)	54 / 317 (17.03%)	
occurrences (all)	26	67	
Rash			
subjects affected / exposed	16 / 155 (10.32%)	105 / 317 (33.12%)	
occurrences (all)	22	147	
Rash maculo-papular			
subjects affected / exposed	5 / 155 (3.23%)	29 / 317 (9.15%)	
occurrences (all)	7	38	
Urticaria			
subjects affected / exposed	4 / 155 (2.58%)	16 / 317 (5.05%)	
occurrences (all)	4	23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 155 (7.74%)	22 / 317 (6.94%)	
occurrences (all)	13	22	
Back pain			
subjects affected / exposed	12 / 155 (7.74%)	23 / 317 (7.26%)	
occurrences (all)	16	24	
Musculoskeletal pain			
subjects affected / exposed	8 / 155 (5.16%)	8 / 317 (2.52%)	
occurrences (all)	9	10	
Myalgia			
subjects affected / exposed	6 / 155 (3.87%)	21 / 317 (6.62%)	
occurrences (all)	7	23	
Pain in extremity			

subjects affected / exposed	8 / 155 (5.16%)	11 / 317 (3.47%)	
occurrences (all)	8	12	
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 155 (8.39%)	22 / 317 (6.94%)	
occurrences (all)	15	26	
Herpes zoster			
subjects affected / exposed	7 / 155 (4.52%)	19 / 317 (5.99%)	
occurrences (all)	7	20	
Lower respiratory tract infection			
subjects affected / exposed	9 / 155 (5.81%)	14 / 317 (4.42%)	
occurrences (all)	12	16	
Nasopharyngitis			
subjects affected / exposed	14 / 155 (9.03%)	17 / 317 (5.36%)	
occurrences (all)	18	18	
Oral candidiasis			
subjects affected / exposed	2 / 155 (1.29%)	17 / 317 (5.36%)	
occurrences (all)	2	20	
Pneumonia			
subjects affected / exposed	2 / 155 (1.29%)	16 / 317 (5.05%)	
occurrences (all)	2	18	
Sinusitis			
subjects affected / exposed	11 / 155 (7.10%)	18 / 317 (5.68%)	
occurrences (all)	11	21	
Upper respiratory tract infection			
subjects affected / exposed	25 / 155 (16.13%)	58 / 317 (18.30%)	
occurrences (all)	34	82	
Urinary tract infection			
subjects affected / exposed	8 / 155 (5.16%)	26 / 317 (8.20%)	
occurrences (all)	8	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	25 / 155 (16.13%)	65 / 317 (20.50%)	
occurrences (all)	36	72	
Hypokalaemia			

subjects affected / exposed	11 / 155 (7.10%)	52 / 317 (16.40%)	
occurrences (all)	14	78	
Hypomagnesaemia			
subjects affected / exposed	2 / 155 (1.29%)	19 / 317 (5.99%)	
occurrences (all)	2	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2013	• Updated information regarding secondary and tertiary endpoints • Updated inclusion criteria relating to contraception • Clarified that the IRC findings would be primary for analyses of PFS and other tumor control endpoints • Updated plan to control Type I error rate for secondary endpoints • Increased washout period for previous cancer therapies from 3 to 6 weeks • Updated language regarding dosing bendamustine to be more consistent with the standard-of-care • Clarified duration of therapy for each study treatment group • Clarified that subjects in Groups A and B who prematurely discontinued 1 study drug could continue the other study drug
17 September 2013	• Revised Exclusion Criteria to exclude patients with known myelodysplasia due to the perceived risk of therapy-related myelodysplastic syndrome, and patients who had contraindications as indicated in the European Levact® Summary of Product Characteristics • Added detailed instructions for monitoring subjects for progressive multifocal leukoencephalopathy • Added initiation of another anticancer therapy as a reason for discontinuation of study drug and study participation • Included an additional formal interim efficacy analysis and changed the timing for the second interim analysis
22 October 2013	• Added monitoring guidelines for subjects who were hepatitis B core-antibody positive at screening
21 October 2014	• Updated guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific AEs • Updated information regarding the interaction of IDL with CYP3A inhibitors, inducers, and substrates

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 March 2016	An increased rate of deaths and serious adverse events (SAEs) among participants with front-line chronic lymphocytic leukemia (CLL) and early-line iNHL treated with idelalisib in combination with standard therapies was observed by the independent data monitoring committee (DMC) during regular review of 3 Gilead Phase 3 studies. Gilead reviewed the unblinded data and terminated this study in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration (FDA). Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	-

Notes:

Limitations and caveats

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

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: