



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia

Summary

EudraCT number	2013-003313-17
Trial protocol	CZ BE HU IT ES PL HR
Global end of trial date	16 June 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	<ul style="list-style-type: none">• Correction of full data setAdding text to "Limitations and Caveats" section

Trial information

Trial identification

Sponsor protocol code	GS-US-312-0123
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01980888
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	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial 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	16 June 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 June 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 progression-free survival in participants with previously untreated chronic lymphocytic leukemia (CLL) who would otherwise be suitable for bendamustine and rituximab treatment as standard of care.

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:

Bendamustine and rituximab

Evidence for comparator: -

Actual start date of recruitment	05 February 2014
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	Poland: 33
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	United States: 60
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Australia: 34

Worldwide total number of subjects	311
EEA total number of subjects	198

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)	153
From 65 to 84 years	158
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the North America, Australia, and Europe. The first participant was screened on 05 February 2014. The last study visit occurred on 16 June 2016.

Pre-assignment

Screening details:

392 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

Arms

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

Idelalisib + bendamustine + rituximab

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:

150 mg administered twice daily

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

Dosage and administration details:

Administered at a starting dose of 90 mg/m² for up to 6 total cycles

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 weekly starting at 375 mg/m² on Day 1 (Week 0) and 500 mg/m² thereafter for a total of 6 cycles

Arm title	Placebo+Bendamustine+Rituximab
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Arm description:

Placebo + bendamustine + rituximab

Arm type	Placebo
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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	Levact
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at a starting dose of 90 mg/m² for up to 6 total cycles

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 weekly starting at 375 mg/m² on Day 1 (Week 0) and 500 mg/m² thereafter for a total of 6 cycles

Number of subjects in period 1	Idelalisib+Bendamustine+Rituximab	Placebo+Bendamustine+Rituximab
Started	157	154
Completed	13	21
Not completed	144	133
Withdrew Consent	17	6
Non- Compliance with Study Drug	3	2
Investigator's Discretion	8	3
Study Terminated by Sponsor	116	122

Baseline characteristics

Reporting groups

Reporting group title	Idelalisib+Bendamustine+Rituximab
Reporting group description: Idelalisib + bendamustine + rituximab	
Reporting group title	Placebo+Bendamustine+Rituximab
Reporting group description: Placebo + bendamustine + rituximab	

Reporting group values	Idelalisib+Bendamustine+Rituximab	Placebo+Bendamustine+Rituximab	Total
Number of subjects	157	154	311
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	64 ± 8.7	63 ± 10	-
Gender categorical Units: Subjects			
Female	57	48	105
Male	100	106	206
Race Units: Subjects			
Asian	1	0	1
Black or African American	1	1	2
White	152	150	302
Other	3	1	4
Not Permitted	0	2	2
Ethnicity Units: Subjects			
Hispanic or Latino	11	2	13
Not Hispanic or Latino	146	149	295
Not Permitted	0	3	3
Rai Stage at Screening			
<p>Rai staging is a way to categorize the disease progression of chronic lymphocytic leukemia (CLL) with higher stages reflecting increasing severity.</p> <p>Rai Stage 0: Lymphocytosis only, Rai Stage I: Lymphocytosis with lymphadenopathy, Rai Stage II: Lymphocytosis with hepatomegaly or splenomegaly, Rai Stage III: Lymphocytosis with anemia, Rai Stage IV: Lymphocytosis with thrombocytopenia.</p>			
Units: Subjects			
Stage I	28	30	58
Stage II	66	58	124
Stage III	25	32	57
Stage IV	38	34	72
IgHV Mutation			
The mutation status of the unique immunoglobulin gene (IgHV) rearrangement in the monoclonal proliferation of B-cells in CLL can be used to predict aggressiveness of the disease. Participants			

with a mutated IgHV gene usually have a less aggressive and more indolent disease, with longer overall survival. Participants with an unmutated IgHV gene usually have a more aggressive disease and shorter overall survival.

Units: Subjects			
Mutated	54	54	108
Unmutated	102	100	202
Missing	1	0	1

17p Deletion in CLL Cells			
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Participants with CLL who have a 17p deletion lack a portion of the chromosome that acts to suppress cancer growth and is a recognized negative prognostic risk factor.

Units: Subjects			
Absent	146	145	291
Present	10	9	19
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Idelalisib+Bendamustine+Rituximab
Reporting group description: Idelalisib + bendamustine + rituximab	
Reporting group title	Placebo+Bendamustine+Rituximab
Reporting group description: Placebo + bendamustine + rituximab	

Primary: Progression-Free Survival

End point title	Progression-Free Survival ^[1]
End point description: Progression-free survival (PFS) is defined as the interval from randomization to the first documentation of definitive disease progression or death from any cause. Definitive disease progression is CLL progression based on standard criteria, excluding lymphocytosis alone. 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 subjects, 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 applicable				

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: Overall Response Rate

End point title	Overall Response Rate
End point description: Overall response rate (ORR) is defined as the proportion of participants who achieve a confirmed complete or partial response. 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 ^[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: Nodal Response Rate

End point title	Nodal Response Rate
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End point description:

Nodal response rate is defined as the proportion of participants who achieve a 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions. Nodal 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
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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: Complete Response Rate

End point title	Complete Response Rate
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End point description:

Complete response rate is defined as the proportion of participants who achieve a confirmed complete response. Complete 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

End point title	Overall Survival
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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

Secondary: Minimal Residual Disease Negativity Rate at Week 36

End point title	Minimal Residual Disease Negativity Rate at Week 36
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End point description:

Minimal residual disease (MRD) negativity rate is defined as the proportion of participants with MRD <

10⁻⁴ assessed by flow cytometry in bone marrow at Week 36 after therapy initiation or at least 12 weeks after the last dose of rituximab or bendamustine (whichever is later) for participants receiving the final dose of rituximab after the original scheduled date. MRD negativity 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 ^[12]	0 ^[13]		
Units: Not applicable				

Notes:

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

[13] - 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 22 months plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants who received at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Idelalisib+Bendamustine+Rituximab
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Reporting group description:

Idelalisib + bendamustine + rituximab

Reporting group title	Placebo+Bendamustine+Rituximab
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Reporting group description:

Placebo + bendamustine + rituximab

Serious adverse events	Idelalisib+Bendamustine+Rituximab	Placebo+Bendamustine+Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 156 (72.44%)	68 / 154 (44.16%)	
number of deaths (all causes)	13	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (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	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	26 / 156 (16.67%)	19 / 154 (12.34%)	
occurrences causally related to treatment / all	24 / 35	18 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unevaluable event			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 156 (0.00%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum sickness			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	5 / 156 (3.21%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Depression			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
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 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 156 (1.92%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
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 / 156 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
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	4 / 156 (2.56%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 156 (0.64%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			

subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 156 (0.64%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 156 (5.13%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	11 / 11	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	29 / 156 (18.59%)	16 / 154 (10.39%)	
occurrences causally related to treatment / all	29 / 33	19 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 156 (4.49%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 156 (1.28%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 156 (3.85%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastritis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
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 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 156 (0.64%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised erythema			
subjects affected / exposed	2 / 156 (1.28%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photosensitivity reaction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	4 / 156 (2.56%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			

subjects affected / exposed	1 / 156 (0.64%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Glucocorticoid deficiency			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
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			
Compartment syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic amyotrophy			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal chest pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (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	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastritis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	3 / 156 (1.92%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (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	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 156 (1.28%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 156 (1.28%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis infectious			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	5 / 156 (3.21%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	11 / 156 (7.05%)	6 / 154 (3.90%)	
occurrences causally related to treatment / all	4 / 11	4 / 9	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 156 (1.92%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	9 / 156 (5.77%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	3 / 9	1 / 2	
deaths causally related to treatment / all	1 / 4	0 / 0	
Septic shock			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strongyloidiasis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tonsillitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
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	1 / 156 (0.64%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 156 (2.56%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	3 / 156 (1.92%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 156 (0.64%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	5 / 156 (3.21%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	5 / 5	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Idelalisib+Bendamustine+Rituximab	Placebo+Bendamustine+Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 156 (98.72%)	150 / 154 (97.40%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 156 (7.05%)	10 / 154 (6.49%)	
occurrences (all)	13	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 156 (13.46%)	9 / 154 (5.84%)	
occurrences (all)	25	10	
Chills			
subjects affected / exposed	21 / 156 (13.46%)	14 / 154 (9.09%)	
occurrences (all)	28	14	
Fatigue			

subjects affected / exposed occurrences (all)	43 / 156 (27.56%) 52	44 / 154 (28.57%) 60	
Mucosal inflammation subjects affected / exposed occurrences (all)	14 / 156 (8.97%) 15	1 / 154 (0.65%) 2	
Oedema peripheral subjects affected / exposed occurrences (all)	19 / 156 (12.18%) 21	16 / 154 (10.39%) 19	
Pyrexia subjects affected / exposed occurrences (all)	71 / 156 (45.51%) 116	38 / 154 (24.68%) 61	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 10	2 / 154 (1.30%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	34 / 156 (21.79%) 47	29 / 154 (18.83%) 36	
Dyspnoea subjects affected / exposed occurrences (all)	24 / 156 (15.38%) 33	12 / 154 (7.79%) 12	
Oropharyngeal pain subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 10	9 / 154 (5.84%) 10	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 12	9 / 154 (5.84%) 9	
Depression subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 8	2 / 154 (1.30%) 3	
Insomnia subjects affected / exposed occurrences (all)	17 / 156 (10.90%) 21	12 / 154 (7.79%) 18	
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	22 / 156 (14.10%) 33	3 / 154 (1.95%) 4	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	18 / 156 (11.54%) 27	2 / 154 (1.30%) 2	
Neutrophil count decreased subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 17	2 / 154 (1.30%) 3	
Weight decreased subjects affected / exposed occurrences (all)	19 / 156 (12.18%) 22	4 / 154 (2.60%) 4	
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	21 / 156 (13.46%) 24	33 / 154 (21.43%) 41	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 9	3 / 154 (1.95%) 4	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	13 / 156 (8.33%) 13	13 / 154 (8.44%) 15	
Dysgeusia subjects affected / exposed occurrences (all)	10 / 156 (6.41%) 11	11 / 154 (7.14%) 12	
Headache subjects affected / exposed occurrences (all)	16 / 156 (10.26%) 22	25 / 154 (16.23%) 28	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	40 / 156 (25.64%) 52	29 / 154 (18.83%) 42	
Neutropenia			

subjects affected / exposed	84 / 156 (53.85%)	90 / 154 (58.44%)	
occurrences (all)	179	180	
Thrombocytopenia			
subjects affected / exposed	19 / 156 (12.18%)	16 / 154 (10.39%)	
occurrences (all)	26	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 156 (8.97%)	14 / 154 (9.09%)	
occurrences (all)	17	17	
Constipation			
subjects affected / exposed	26 / 156 (16.67%)	34 / 154 (22.08%)	
occurrences (all)	33	45	
Diarrhoea			
subjects affected / exposed	63 / 156 (40.38%)	46 / 154 (29.87%)	
occurrences (all)	111	72	
Dry mouth			
subjects affected / exposed	11 / 156 (7.05%)	4 / 154 (2.60%)	
occurrences (all)	11	4	
Dyspepsia			
subjects affected / exposed	15 / 156 (9.62%)	12 / 154 (7.79%)	
occurrences (all)	16	17	
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 156 (5.77%)	4 / 154 (2.60%)	
occurrences (all)	9	4	
Nausea			
subjects affected / exposed	61 / 156 (39.10%)	63 / 154 (40.91%)	
occurrences (all)	102	95	
Stomatitis			
subjects affected / exposed	10 / 156 (6.41%)	4 / 154 (2.60%)	
occurrences (all)	12	4	
Vomiting			
subjects affected / exposed	37 / 156 (23.72%)	23 / 154 (14.94%)	
occurrences (all)	61	31	
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed occurrences (all)	14 / 156 (8.97%) 16	4 / 154 (2.60%) 5	
Erythema subjects affected / exposed occurrences (all)	12 / 156 (7.69%) 17	8 / 154 (5.19%) 10	
Pruritus subjects affected / exposed occurrences (all)	24 / 156 (15.38%) 27	32 / 154 (20.78%) 36	
Rash subjects affected / exposed occurrences (all)	63 / 156 (40.38%) 87	34 / 154 (22.08%) 53	
Rash macular subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 8	2 / 154 (1.30%) 2	
Rash maculo-papular subjects affected / exposed occurrences (all)	29 / 156 (18.59%) 40	12 / 154 (7.79%) 14	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	9 / 156 (5.77%) 9	3 / 154 (1.95%) 3	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	16 / 156 (10.26%) 18	12 / 154 (7.79%) 13	
Back pain subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 12	18 / 154 (11.69%) 18	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	5 / 156 (3.21%) 5	8 / 154 (5.19%) 8	
Influenza subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 6	8 / 154 (5.19%) 9	
Nasopharyngitis			

subjects affected / exposed	8 / 156 (5.13%)	14 / 154 (9.09%)	
occurrences (all)	8	21	
Oral candidiasis			
subjects affected / exposed	8 / 156 (5.13%)	4 / 154 (2.60%)	
occurrences (all)	8	4	
Oral herpes			
subjects affected / exposed	5 / 156 (3.21%)	8 / 154 (5.19%)	
occurrences (all)	7	9	
Pneumonia			
subjects affected / exposed	10 / 156 (6.41%)	3 / 154 (1.95%)	
occurrences (all)	11	3	
Respiratory tract infection			
subjects affected / exposed	9 / 156 (5.77%)	4 / 154 (2.60%)	
occurrences (all)	14	4	
Sinusitis			
subjects affected / exposed	9 / 156 (5.77%)	4 / 154 (2.60%)	
occurrences (all)	9	4	
Upper respiratory tract infection			
subjects affected / exposed	25 / 156 (16.03%)	21 / 154 (13.64%)	
occurrences (all)	32	29	
Urinary tract infection			
subjects affected / exposed	15 / 156 (9.62%)	6 / 154 (3.90%)	
occurrences (all)	15	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 156 (16.67%)	21 / 154 (13.64%)	
occurrences (all)	32	26	
Dehydration			
subjects affected / exposed	12 / 156 (7.69%)	2 / 154 (1.30%)	
occurrences (all)	17	3	
Hypokalaemia			
subjects affected / exposed	25 / 156 (16.03%)	4 / 154 (2.60%)	
occurrences (all)	33	5	
Hypophosphataemia			
subjects affected / exposed	9 / 156 (5.77%)	0 / 154 (0.00%)	
occurrences (all)	10	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2014	The following changes were to align with the bendamustine and rituximab Summary of Product Characteristics (SmPC): <ul style="list-style-type: none">• To align the protocol with the male contraceptive requirements in the SmPC for bendamustine• To exclude subjects with known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for idelalisib, bendamustine, or rituximab• To exclude subjects who received yellow fever vaccine within 30 days prior to randomization• To exclude subjects who have undergone major surgery within 30 days prior to randomization• To include information regarding the use of live vaccines• To refer investigators to local prescribing guidelines for each specific concomitant medicine with potential for safety considerations and discuss any questions with the Gilead Medical Monitor before initiation of such treatments
06 November 2014	To change MRD from a primary to a secondary endpoint, update to the guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events, and revisions to the information regarding the interaction of idelalisib and 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 CLL and early-line indolent non-Hodgkin lymphoma (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:

