



Clinical trial results:

Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent or aggressive Non-Hodgkin's lymphomas

Summary

EudraCT number	2012-002602-52
Trial protocol	GB FI DE BE ES IT SE PL AT PT HU DK IE GR LU
Global end of trial date	18 May 2023

Results information

Result version number	v1 (current)
This version publication date	29 May 2024
First version publication date	29 May 2024

Trial information

Trial identification

Sponsor protocol code	BAY80-6946/16349
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01660451
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, 49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, 49 30 300139003, clinical-trials-contact@bayer.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	18 May 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of study part A was to evaluate the efficacy and safety of copanlisib in patients with indolent or aggressive NHL who have progressed after standard therapy. The objective of study part B was to evaluate the efficacy and safety of copanlisib in patients with indolent B-cell NHL relapsed after, or refractory to widely used approved therapies in standard practice.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Australia: 3

Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Türkiye: 10
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	338
EEA total number of subjects	200

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)	162
From 65 to 84 years	170
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Part A-Study enrolled subjects from 41 study centers in 10 countries, between 19 NOV 2012 (first subject first visit [FPFV]) and 13 AUG 2018 (last subject last visit [LPLV]). Part B-Study enrolled subjects from 81 study centers in 24 countries, between 04 NOV 2013 (FPFV) and 18 MAY 2023 (LPLV),

Pre-assignment

Screening details:

Part A: 125 subjects were screened, 41 were screened but never assigned to treatment. Total 84 were assigned to treatment. Part B: 213 subjects were screened, 70 were screened but never assigned to treatment. Total 143 were assigned to treatment, of them 1 was suspected as fraudulent and excluded from analysis sets. Therefore 142 were evaluable.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Indolent NHL/CLL

Arm description:

Subjects with indolent Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Arm type	Experimental
Investigational medicinal product name	Copanlisib (Aliqopa)
Investigational medicinal product code	BAY80-6946
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing was weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (i.e., no infusion on Day 22).

Arm title	Part A: Aggressive NHL
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Arm description:

Subjects with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Arm type	Experimental
Investigational medicinal product name	Copanlisib (Aliqopa)
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing was weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (i.e., no infusion on Day 22).

Arm title	Part B: Indolent NHL
Arm description: Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.	
Arm type	Experimental
Investigational medicinal product name	Copanlisib (Aliqopa)
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing was weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (i.e., no infusion on Day 22).

Number of subjects in period 1 ^[1]	Part A: Indolent NHL/CLL	Part A: Aggressive NHL	Part B: Indolent NHL
Started	33	51	142
Completed	0	0	0
Not completed	33	51	142
Progressive disease – radiological progression	12	23	50
Physician decision	1	2	5
Trial closure	-	-	1
Protocol Deviation	-	-	1
AE not related to clinical disease progression	13	10	40
Progressive disease – clinical progression	4	10	9
Consent withdrawn by subject	1	1	20
Death	1	-	1
Other	-	-	1
AE related to clinical disease progression	1	3	11
Switching to other therapy	-	1	1
Sponsor Decision	-	-	1
Protocol deviation	-	1	1

Notes:

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

Justification: In study part A, 125 subjects were screened, 41 were screened but never assigned to treatment, total 84 were assigned to treatment. In study part B, 213 subjects were screened, 70 were screened but never assigned to treatment, total 143 were assigned to treatment, of them 1 was suspected as fraudulent and excluded from analysis sets. Therefore 142 were evaluable.

Baseline characteristics

Reporting groups

Reporting group title	Part A: Indolent NHL/CLL
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Reporting group description:

Subjects with indolent Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Reporting group title	Part A: Aggressive NHL
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Reporting group description:

Subjects with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Reporting group title	Part B: Indolent NHL
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Reporting group description:

Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Reporting group values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL	Part B: Indolent NHL
Number of subjects	33	51	142
Age categorical			
Units: Subjects			
Adults (18-64 years)	11	27	78
From 65-84 years	21	22	64
85 years and over	1	2	0
Age continuous			
Units: years			
arithmetic mean	66.7	62.2	61.4
standard deviation	± 9.8	± 15.5	± 12.1
Gender categorical			
Units: Subjects			
Female	18	22	71
Male	15	29	71
Race			
Units: Subjects			
Asian	0	0	15
White	25	40	120
Unknown or Not Reported	8	11	7
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	2	6
Not Hispanic or Latino	21	36	124
Unknown or Not Reported	10	13	12

Reporting group values	Total		
Number of subjects	226		
Age categorical Units: Subjects			
Adults (18-64 years)	116		
From 65-84 years	107		
85 years and over	3		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	111		
Male	115		
Race Units: Subjects			
Asian	15		
White	185		
Unknown or Not Reported	26		
Ethnicity Units: Subjects			
Hispanic or Latino	10		
Not Hispanic or Latino	181		
Unknown or Not Reported	35		

End points

End points reporting groups

Reporting group title	Part A: Indolent NHL/CLL
Reporting group description: Subjects with indolent Non-Hodgkin's Lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.	
Reporting group title	Part A: Aggressive NHL
Reporting group description: Subjects with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.	
Reporting group title	Part B: Indolent NHL
Reporting group description: Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.	
Subject analysis set title	Full analysis set (FAS) - Part A
Subject analysis set type	Full analysis
Subject analysis set description: All subjects assigned to study treatment.	
Subject analysis set title	Full analysis set (FAS) - Part B
Subject analysis set type	Full analysis
Subject analysis set description: All subjects assigned to study treatment.	
Subject analysis set title	Safety analysis set (SAF)-Part A
Subject analysis set type	Safety analysis
Subject analysis set description: All FAS subjects with at least one study drug administration.	
Subject analysis set title	Safety analysis set (SAF)-Part B
Subject analysis set type	Safety analysis
Subject analysis set description: All FAS subjects with at least one study drug administration.	
Subject analysis set title	Per protocol set (PPS)- Part A
Subject analysis set type	Per protocol
Subject analysis set description: All subjects with drug administration that were evaluable for objective tumor response (OR) and that had no major protocol deviation effecting the primary efficacy evaluation. At least one post baseline tumor assessment was available in order to consider the patient evaluable. Subjects who were not evaluable for tumor response and who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated were also to be considered evaluable. The detailed definitions and the assignment of subjects to this analysis set were based on the Validity Review Meeting.	

Primary: Objective Response Rate (ORR) Based on Independent Review-Part A

End point title	Objective Response Rate (ORR) Based on Independent Review-Part A ^{[1][2]}
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End point description:

Objective response rate was defined as the proportion of participants with a best response rating of complete response (CR), unconfirmed complete response (CRu) or partial response (PR), based on the Report of an International Workshop to Standardize Response Criteria for non-Hodgkins Lymphomas, Cheson, 1999, as evaluated by the Independent Response Adjudication Committee (IRAC). For chronic lymphocytic leukemia (CLL) patients Hallek criteria (2008) were used and assessed by investigator.

End point type	Primary
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End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

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: Descriptive statistics were done, no inferential statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 ^[3]	48 ^[4]		
Units: Percentage				
number (confidence interval 90%)	43.75 (28.73 to 59.68)	27.08 (16.83 to 39.57)		

Notes:

[3] - PPS

[4] - PPS

Statistical analyses

No statistical analyses for this end point

Primary: ORR Based on Independent Review-Part B

End point title	ORR Based on Independent Review-Part B ^{[5][6]}
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End point description:

Objective response rate was defined as the proportion of participants with a best response rating of CR or PR, based on the International Working Group Revised response Criteria for Malignant Lymphoma, Cheson 2007.

End point type	Primary
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End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

Notes:

[5] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	142 ^[7]			
Units: Percentage				
number (confidence interval 95%)	59.15 (50.60 to 67.32)			

Notes:

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: ORR Based on Investigator Assessment-Part A

End point title	ORR Based on Investigator Assessment-Part A ^{[8][9]}
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End point description:

Objective response rate was defined as the proportion of participants with a best response rating of CR, CRu or PR, based on the Report of an International Workshop to Standardize Response Criteria for non-Hodgkins Lymphomas, Cheson, 1999. For CLL patients Hallek criteria (2008) were used and assessed by investigator.

End point type	Primary
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End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

Notes:

[8] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 ^[10]	48 ^[11]		
Units: Percentage				
number (confidence interval 90%)	46.88 (31.54 to 62.66)	31.25 (20.35 to 43.97)		

Notes:

[10] - PPS

[11] - PPS

Statistical analyses

No statistical analyses for this end point

Primary: ORR Based on Investigator Assessment-Part B

End point title	ORR Based on Investigator Assessment-Part B ^{[12][13]}
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End point description:

Objective response rate was defined as the proportion of participants with a best response rating of CR or PR, based on the International Working Group Revised response Criteria for Malignant Lymphoma, Cheson 2007.

End point type	Primary
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End point timeframe:

Baseline up to the last patient has completed the 16 weeks of treatment

Notes:

[12] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	142 ^[14]			
Units: Percentage				
number (confidence interval 95%)	51.41 (42.88 to 59.87)			

Notes:

[14] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Based on Independent Review-Part A

End point title	Duration of Response (DOR) Based on Independent Review-Part A ^[15]
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End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression. "99999" denotes value can't be estimated.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 6 years

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14 ^[16]	14 ^[17]		
Units: Days				
median (confidence interval 95%)	322 (61 to 99999)	99999 (61 to 99999)		

Notes:

[16] - PPS

[17] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Based on Independent Review-Part B

End point title | DOR Based on Independent Review-Part B^[18]

End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression."

End point type | Secondary

End point timeframe:

Baseline up to approximately 10 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	85 ^[19]			
Units: Months				
median (confidence interval 95%)	14.9 (9.2 to 22.6)			

Notes:

[19] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Based on Investigator Assessment-Part A

End point title | DOR Based on Investigator Assessment-Part A^[20]

End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression." "99999" denotes value can't be estimated.

End point type | Secondary

End point timeframe:

Baseline up to approximately 6 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15 ^[21]	15 ^[22]		
Units: Days				
median (confidence interval 95%)	189 (56 to 574)	190 (112 to 99999)		

Notes:

[21] - PPS

[22] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Based on Independent Review-Part B

End point title	PFS Based on Independent Review-Part B ^[23]
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End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

End point type	Secondary
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End point timeframe:

Baseline up to approximately 10 years

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: Months				
median (confidence interval 95%)	11.3 (8.1 to 17.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Based on Investigator Assessment-Part A

End point title	PFS Based on Investigator Assessment-Part A ^[24]
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End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

End point type	Secondary
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End point timeframe:

Baseline up to approximately 6 years

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[25]	51 ^[26]		
Units: Days				
median (confidence interval 95%)	224 (172 to 419)	70 (47 to 115)		

Notes:

[25] - FAS

[26] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Based on Independent Review-Part A

End point title	Progression Free Survival (PFS) Based on Independent Review-Part A ^[27]
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End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

End point type	Secondary
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End point timeframe:

Baseline up to approximately 6 years

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[28]	51 ^[29]		
Units: Days				
median (confidence interval 95%)	223 (147 to 546)	70 (47 to 115)		

Notes:

[28] - FAS

[29] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Based on Investigator Assessment-Part B

End point title	DOR Based on Investigator Assessment-Part B ^[30]
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End point description:

Duration of response (DOR) was defined as the time (in days) from the date of the first observed tumor response of CR or PR (whichever was noted earlier) to first subsequent disease progression (either first progressive disease [PD], first clinical progression or first adverse event [AE] associated with clinical disease progression) or death caused by disease progression, if this death occurred before progression was documented. All deaths were considered as 'caused by disease progression' except deaths with the reason "other" or "AE not related to disease progression."

End point type Secondary

End point timeframe:

Baseline up to approximately 10 years

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	78 ^[31]			
Units: Months				
median (confidence interval 95%)	11.5 (9.2 to 16.1)			

Notes:

[31] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Based on Investigator Assessment-Part B

End point title PFS Based on Investigator Assessment-Part B^[32]

End point description:

PFS was defined as the time (in days) from the date of the first treatment to the date of first observed PD (radiological or clinical, or first AE associated with clinical PD, whichever was earlier) or death due to any cause (if death occurred before progression was documented).

End point type Secondary

End point timeframe:

Baseline up to approximately 10 years

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	142 ^[33]			
Units: Months				
median (confidence interval 95%)	10.8 (7.2 to 12.8)			

Notes:

[33] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy – Lymphoma Lymphoma Subscale (FACT-Lym LymS) at Week 16 - Part B

End point title	Functional Assessment of Cancer Therapy – Lymphoma Lymphoma Subscale (FACT-Lym LymS) at Week 16 - Part B ^[34]
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End point description:

HRQoL assessment was used to describe development of patients with copanlisib by using FACT-Lym questionnaire assessment tool. It contains 42 items (questions) covering HRQoL, common lymphoma symptoms and treatment side-effects. The FACT - General (FACT-G) questionnaire contains 27 items covering 4 core HRQoL subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 items) (FACT-Lym LymS), addressing issues typically experienced by lymphoma patients. Some of the issues covered include pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. FACT-Lym also asks patients about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. Score range for the FACT-Lym LymS was 0 - 60, higher score represent less symptoms. Here in below table "n" signifies evaluable participants for the respective category.

End point type	Secondary
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End point timeframe:

Baseline up to week 16

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	141 ^[35]			
Units: units on a scale				
median (inter-quartile range (Q1-Q3))				
Baseline	46.50 (40.50 to 52.00)			
Value at Week 16	49.00 (42.00 to 54.00)			

Notes:

[35] - FAS; Baseline N=132; Week 16 N=141

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)-Part A

End point title	Overall Survival (OS)-Part A ^[36]
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End point description:

OS was defined as the time (in days) from the date of first administration of study treatment to death due to any cause. "99999" denotes value can't be estimated.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 6 years

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part A arms.

End point values	Part A: Indolent NHL/CLL	Part A: Aggressive NHL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[37]	51 ^[38]		
Units: Days				
median (confidence interval 95%)	657 (391 to 99999)	211 (140 to 399)		

Notes:

[37] - FAS

[38] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: OS-Part B

End point title	OS-Part B ^[39]
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End point description:

OS was defined as the time (in days) from the date of first administration of study treatment to death due to any cause. "99999" denotes value can't be estimated.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 10 years

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	142 ^[40]			
Units: Months				
median (confidence interval 95%)	59.1 (36.5 to 99999)			

Notes:

[40] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) total score at Week 16 - Part B

End point title	Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) total score at Week 16 - Part B ^[41]
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End point description:

HRQoL assessment was used to describe development of patients with copanlisib by using FACT-Lym questionnaire assessment tool. It contains 42 items (questions) covering HRQoL, common lymphoma symptoms and treatment side-effects. The FACT - General (FACT-G) questionnaire contains 27 items covering 4 core HRQoL subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 items) (FACT-Lym LymS), addressing issues typically experienced by lymphoma patients. Some of the issues covered include pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. FACT-Lym also asks patients about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. FACT-Lym total score range was 0-168, higher score indicates better HRQoL. Here, in the below table "n" signifies evaluable participants for the respective category.

End point type	Secondary
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End point timeframe:

Baseline up to week 16

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for part B arms.

End point values	Part B: Indolent NHL			
Subject group type	Reporting group			
Number of subjects analysed	141 ^[42]			
Units: units on a scale				
median (inter-quartile range (Q1-Q3))				
Baseline	127.50 (113.75 to 145.75)			
Value at Week 16	130.83 (113.33 to 146.50)			

Notes:

[42] - FAS; Baseline N=132; Week 16 N=141

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first study intervention up to 35 days after the end of study intervention, Part A: approximately 6 years. Part B: approximately 10 years.

Adverse event reporting additional description:

Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, Part A: approximately 6 years. Part B: approximately 10 years.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Part A: Indolent NHL/CLL
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Reporting group description:

Participants with indolent Non-Hodgkin's lymphoma/Chronic lymphocytic leukemia [iNHL/CLL] received copanlisib 0.8 milligram per kilogram (mg/kg), maximum 65 mg, intravenous (IV) infusion dosing over 1 hour in 100 milliliter (mL) normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Reporting group title	Part B: Indolent NHL
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Reporting group description:

Subjects with indolent B-cell NHL received copanlisib fixed 60 mg or 0.8 mg/kg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Revised Response Criteria for Malignant Lymphoma by Cheson et al., 2007, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Reporting group title	Part A: Aggressive NHL
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Reporting group description:

Participants with aggressive NHL (aNHL) received copanlisib 0.8 mg/kg, maximum 65 mg, IV infusion dosing over 1 hour in 100 mL normal saline solution on Days 1, 8, and 15 of a 28-day treatment cycle until occurrence of progressive disease, as defined in the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas by Cheson et al. 1999, clinical progression, unacceptable toxicity, or any other criteria meeting withdrawal from study.

Serious adverse events	Part A: Indolent NHL/CLL	Part B: Indolent NHL	Part A: Aggressive NHL
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 33 (48.48%)	81 / 142 (57.04%)	31 / 51 (60.78%)
number of deaths (all causes)	21	75	39
number of deaths resulting from adverse events	3	6	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour compression			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Porocarcinoma			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour flare			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Superficial vein thrombosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Preoperative care			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	1 / 33 (3.03%)	2 / 142 (1.41%)	4 / 51 (7.84%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 33 (3.03%)	9 / 142 (6.34%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza like illness			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Scrotal swelling			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 142 (4.23%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Organising pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Disorientation			

subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 33 (3.03%)	2 / 142 (1.41%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Biliary-vascular fistula			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Afferent loop syndrome			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aortic valve incompetence			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 33 (3.03%)	3 / 142 (2.11%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	1 / 1	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancytopenia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 142 (2.82%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	4 / 142 (2.82%)	3 / 51 (5.88%)
occurrences causally related to treatment / all	0 / 0	3 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Gallbladder obstruction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 33 (3.03%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal impairment			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 33 (12.12%)	20 / 142 (14.08%)	4 / 51 (7.84%)
occurrences causally related to treatment / all	2 / 4	20 / 25	5 / 5
deaths causally related to treatment / all	0 / 0	1 / 2	1 / 1
Pyelonephritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lower respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	3 / 51 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Influenza			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cryptococcosis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis aspergillus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 142 (0.70%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 142 (1.41%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 142 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 33 (3.03%)	7 / 142 (4.93%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	9 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part A: Indolent NHL/CLL	Part B: Indolent NHL	Part A: Aggressive NHL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	138 / 142 (97.18%)	50 / 51 (98.04%)
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 33 (69.70%)	42 / 142 (29.58%)	24 / 51 (47.06%)
occurrences (all)	94	330	82
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 33 (48.48%)	36 / 142 (25.35%)	14 / 51 (27.45%)
occurrences (all)	20	41	15
Chills			
subjects affected / exposed	2 / 33 (6.06%)	12 / 142 (8.45%)	1 / 51 (1.96%)
occurrences (all)	2	13	1
Chest pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 142 (1.41%)	3 / 51 (5.88%)
occurrences (all)	1	2	4
Influenza like illness			
subjects affected / exposed	2 / 33 (6.06%)	6 / 142 (4.23%)	2 / 51 (3.92%)
occurrences (all)	2	6	2
Asthenia			
subjects affected / exposed	8 / 33 (24.24%)	11 / 142 (7.75%)	6 / 51 (11.76%)
occurrences (all)	13	14	6
Mucosal inflammation			
subjects affected / exposed	4 / 33 (12.12%)	10 / 142 (7.04%)	6 / 51 (11.76%)
occurrences (all)	5	17	8
Oedema peripheral			
subjects affected / exposed	3 / 33 (9.09%)	12 / 142 (8.45%)	2 / 51 (3.92%)
occurrences (all)	7	14	2

Pyrexia			
subjects affected / exposed	10 / 33 (30.30%)	35 / 142 (24.65%)	8 / 51 (15.69%)
occurrences (all)	14	54	22
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 33 (6.06%)	4 / 142 (2.82%)	2 / 51 (3.92%)
occurrences (all)	2	5	3
Productive cough			
subjects affected / exposed	3 / 33 (9.09%)	10 / 142 (7.04%)	3 / 51 (5.88%)
occurrences (all)	3	12	3
Nasal congestion			
subjects affected / exposed	2 / 33 (6.06%)	4 / 142 (2.82%)	0 / 51 (0.00%)
occurrences (all)	3	5	0
Epistaxis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 142 (0.00%)	3 / 51 (5.88%)
occurrences (all)	4	0	3
Dyspnoea exertional			
subjects affected / exposed	3 / 33 (9.09%)	4 / 142 (2.82%)	1 / 51 (1.96%)
occurrences (all)	3	4	1
Dyspnoea			
subjects affected / exposed	4 / 33 (12.12%)	11 / 142 (7.75%)	4 / 51 (7.84%)
occurrences (all)	4	11	4
Cough			
subjects affected / exposed	7 / 33 (21.21%)	27 / 142 (19.01%)	6 / 51 (11.76%)
occurrences (all)	13	45	6
Oropharyngeal pain			
subjects affected / exposed	1 / 33 (3.03%)	15 / 142 (10.56%)	2 / 51 (3.92%)
occurrences (all)	1	20	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 33 (0.00%)	8 / 142 (5.63%)	3 / 51 (5.88%)
occurrences (all)	0	8	3
Anxiety			
subjects affected / exposed	0 / 33 (0.00%)	4 / 142 (2.82%)	3 / 51 (5.88%)
occurrences (all)	0	5	3
Investigations			

Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	6 / 142 (4.23%) 6	4 / 51 (7.84%) 5
Blood glucose increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 5	2 / 142 (1.41%) 42	0 / 51 (0.00%) 0
Eosinophil count increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 142 (0.00%) 0	1 / 51 (1.96%) 1
Lipase increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 4	8 / 142 (5.63%) 9	2 / 51 (3.92%) 2
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 15	7 / 142 (4.93%) 19	1 / 51 (1.96%) 2
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5	13 / 142 (9.15%) 16	4 / 51 (7.84%) 4
Weight decreased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	9 / 142 (6.34%) 9	2 / 51 (3.92%) 2
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	8 / 142 (5.63%) 8	0 / 51 (0.00%) 0
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 142 (1.41%) 2	0 / 51 (0.00%) 0
Nervous system disorders Taste disorder subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 142 (0.70%) 1	1 / 51 (1.96%) 1
Somnolence subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 142 (0.00%) 0	0 / 51 (0.00%) 0
Paraesthesia			

subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	4 / 142 (2.82%) 5	1 / 51 (1.96%) 1
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	6 / 142 (4.23%) 6	3 / 51 (5.88%) 3
Headache subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 9	14 / 142 (9.86%) 22	9 / 51 (17.65%) 12
Dizziness subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4	4 / 142 (2.82%) 5	3 / 51 (5.88%) 4
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	11 / 33 (33.33%) 21	27 / 142 (19.01%) 43	12 / 51 (23.53%) 13
Lymphopenia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	8 / 142 (5.63%) 16	0 / 51 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	21 / 142 (14.79%) 30	3 / 51 (5.88%) 3
Neutropenia subjects affected / exposed occurrences (all)	9 / 33 (27.27%) 12	40 / 142 (28.17%) 117	15 / 51 (29.41%) 25
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 142 (0.00%) 0	1 / 51 (1.96%) 1
Gastrointestinal disorders			
Dry mouth subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	1 / 142 (0.70%) 1	3 / 51 (5.88%) 3
Diarrhoea subjects affected / exposed occurrences (all)	13 / 33 (39.39%) 65	51 / 142 (35.92%) 98	21 / 51 (41.18%) 39
Constipation			

subjects affected / exposed	5 / 33 (15.15%)	18 / 142 (12.68%)	8 / 51 (15.69%)
occurrences (all)	7	21	11
Abdominal pain upper			
subjects affected / exposed	3 / 33 (9.09%)	11 / 142 (7.75%)	3 / 51 (5.88%)
occurrences (all)	4	16	3
Abdominal pain			
subjects affected / exposed	4 / 33 (12.12%)	10 / 142 (7.04%)	1 / 51 (1.96%)
occurrences (all)	6	10	1
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 33 (6.06%)	5 / 142 (3.52%)	2 / 51 (3.92%)
occurrences (all)	2	5	2
Vomiting			
subjects affected / exposed	5 / 33 (15.15%)	20 / 142 (14.08%)	5 / 51 (9.80%)
occurrences (all)	10	25	7
Stomatitis			
subjects affected / exposed	4 / 33 (12.12%)	14 / 142 (9.86%)	4 / 51 (7.84%)
occurrences (all)	6	24	4
Oral pain			
subjects affected / exposed	0 / 33 (0.00%)	3 / 142 (2.11%)	3 / 51 (5.88%)
occurrences (all)	0	3	3
Nausea			
subjects affected / exposed	10 / 33 (30.30%)	33 / 142 (23.24%)	18 / 51 (35.29%)
occurrences (all)	17	45	22
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 33 (3.03%)	7 / 142 (4.93%)	3 / 51 (5.88%)
occurrences (all)	1	10	3
Rash			
subjects affected / exposed	5 / 33 (15.15%)	14 / 142 (9.86%)	6 / 51 (11.76%)
occurrences (all)	6	31	8
Pruritus			
subjects affected / exposed	3 / 33 (9.09%)	14 / 142 (9.86%)	3 / 51 (5.88%)
occurrences (all)	3	37	5
Hyperhidrosis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 142 (0.00%)	1 / 51 (1.96%)
occurrences (all)	2	0	1

Erythema subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	2 / 142 (1.41%) 3	3 / 51 (5.88%) 3
Eczema subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4	4 / 142 (2.82%) 10	2 / 51 (3.92%) 2
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 142 (1.41%) 2	0 / 51 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 10	12 / 142 (8.45%) 17	3 / 51 (5.88%) 5
Back pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 4	14 / 142 (9.86%) 22	4 / 51 (7.84%) 4
Arthralgia subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 6	14 / 142 (9.86%) 15	5 / 51 (9.80%) 5
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 10	16 / 142 (11.27%) 22	5 / 51 (9.80%) 8
Conjunctivitis subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	6 / 142 (4.23%) 9	1 / 51 (1.96%) 2
Cystitis subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 5	1 / 142 (0.70%) 1	1 / 51 (1.96%) 1
Herpes zoster subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 142 (2.11%) 4	1 / 51 (1.96%) 1
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	4 / 142 (2.82%) 5	3 / 51 (5.88%) 6

Nasopharyngitis			
subjects affected / exposed	1 / 33 (3.03%)	9 / 142 (6.34%)	2 / 51 (3.92%)
occurrences (all)	2	16	2
Oral candidiasis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 142 (4.23%)	3 / 51 (5.88%)
occurrences (all)	0	7	3
Pneumonia			
subjects affected / exposed	3 / 33 (9.09%)	12 / 142 (8.45%)	2 / 51 (3.92%)
occurrences (all)	3	14	2
Rhinitis			
subjects affected / exposed	1 / 33 (3.03%)	9 / 142 (6.34%)	1 / 51 (1.96%)
occurrences (all)	1	13	1
Sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	10 / 142 (7.04%)	2 / 51 (3.92%)
occurrences (all)	1	13	4
Upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)	22 / 142 (15.49%)	2 / 51 (3.92%)
occurrences (all)	2	45	2
Urinary tract infection			
subjects affected / exposed	6 / 33 (18.18%)	7 / 142 (4.93%)	7 / 51 (13.73%)
occurrences (all)	6	10	7
Oral herpes			
subjects affected / exposed	1 / 33 (3.03%)	9 / 142 (6.34%)	2 / 51 (3.92%)
occurrences (all)	2	13	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 33 (15.15%)	15 / 142 (10.56%)	7 / 51 (13.73%)
occurrences (all)	6	15	8
Hypophosphataemia			
subjects affected / exposed	2 / 33 (6.06%)	4 / 142 (2.82%)	4 / 51 (7.84%)
occurrences (all)	2	10	4
Hyperglycaemia			
subjects affected / exposed	21 / 33 (63.64%)	71 / 142 (50.00%)	27 / 51 (52.94%)
occurrences (all)	88	515	55
Hypokalaemia			

subjects affected / exposed	2 / 33 (6.06%)	11 / 142 (7.75%)	5 / 51 (9.80%)
occurrences (all)	3	11	5
Hypomagnesaemia			
subjects affected / exposed	1 / 33 (3.03%)	10 / 142 (7.04%)	2 / 51 (3.92%)
occurrences (all)	1	11	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2013	Amendment 2: Inclusion criteria: the wording of the inclusion criterion applicable for patients with aggressive NHL was slightly changed to clarify that patients who failed first line chemo /immunotherapy but who were not eligible for a high dose regimen followed by transplant were considered suitable for the study even if they had undergone only one previous treatment. Introduction of mandatory collection of archival tumor tissue for biomarker analysis. Introduction of the ECG sub-study at the request of Food and Drug Administration (FDA). Exclusion criteria: Patients affected by central nervous system lymphoma involvement were excluded from the study. Clarification of the requirement to perform CT/MRI to all suspected sites of disease. Clarification of the tumor response evaluation criteria: CT/MRI was to be required at EOT if a patient discontinued due to progressive disease in order to radiologically assess such progression. Imaging was not required if progressive disease was radiologically evaluated within previous 4 weeks. Inclusion of interstitial lung disease and pneumonitis as AEs of special safety interest based on recently available data from Phase I studies.
28 March 2013	Amendment 3: Introduction of study Part B: New cohort (extension cohort) of patients with FL was added (further changes related only to study Part B are not listed below). Introduction of mandatory collection of fresh biopsies from patients with aggressive lymphoma. Introduction of the possibility to re-screen patients. Replacement criteria: Patients whose participation was terminated due to disease progression before the first evaluable post-baseline tumor evaluation could be replaced. Specification of validity of signed informed consent: It was clarified that the maximum allowed interval between signing of informed consent and start of treatment was 28 days. Inclusion and exclusion criteria: patients with transformed indolent lymphoma must have received at least 2 prior chemotherapy- and/or immunotherapy-based regimens. The measurable lesion must not have been previously irradiated. Inclusion criterion related to alkaline phosphatase was removed. Exclusion criterion related to dehydration was removed. Open biopsy was excluded within the previous 7 days before start of study medication. Wording of the exclusion criterion referring to pheochromocytoma was clarified. Changes in the laboratory analyses: Bands were removed as a parameter for differential white blood cell count and turbidity was added to the urinalysis parameters. Urea could now be measured alternatively to BUN (blood urea nitrogen) if BUN was not routinely measured at the site. Additional PK sampling was added for patients participating in the ECG sub-study.

17 February 2014	Amendment 4: following modifications applicable to study Part A: It was specified that the end of the safety follow-up would take place 35 days after the last study drug administration. Inclusion criteria: An additional T-cell histotype was added to the inclusion criteria for patients with aggressive NHL and a previously existing histotype was further specified according to the World Health Organization (WHO) classification. Exclusion criteria: The requirement for laboratory screening for hepatitis B and C to be carried out up to 28 days before starting the study drug administration was added. Text was included which only allowed the use of short acting insulin for the treatment of transient hyperglycemia and not permitting prophylactic administration of short acting insulin prior to copanlisib infusion. Dose modification guidance was clarified in case of skin toxicity (since some rash events were reported in Part A of the study) and non-infectious pneumonitis. Additional assessments were included for hepatitis to be performed 28 days prior to the first administration of study drug to be consistent with the protocol's exclusion criteria regarding known history of chronic hepatitis B or C. Statistical analysis text regarding additional aggressive NHL patients was amended. Data for these patients was to be analyzed separately from the patients in the primary analysis, i.e., 16 weeks after the last of these patients started treatment. In addition, these patients were to be analyzed in separate FAS (full analysis set), SAF (safety analysis set) and PPS (per protocol set) analysis sets. Definition of duration of response (DOR) was amended to state that duration of response is defined as the time from the date of first observed tumor response (CR or PR) until first subsequent disease progression or until death "due to any cause". In addition, unconfirmed responses were also to be included in the analysis.
04 July 2014	Amendment 5: following modifications applicable to study Part A: Collection of tumor tissue was clarified: For patients with aggressive NHL, fresh tissue was mandatory. For all patients: If the patient has undergone a fresh biopsy for any reason and archival tumor tissue is not available, fresh biopsy is sufficient for central pathology review and biomarker analysis. The text describing conditions for withdrawal from study treatment was clarified to reduce occurrence of screening failures. In addition, withdrawal criterion for drug-induced pancreatitis was added. It was clarified that phenytoin, carbamazepine and phenobarbital were prohibited medications. Text regarding AEs of special safety interest was clarified. Unspecific interstitial lung disease (ILD) was removed as it had not been observed within the copanlisib program. All observed cases of ILD were likely attributable to non-infectious pneumonitis, which remained as an AE of special safety interest.
25 August 2015	Amendment 7: It introduced changes to the Part B integrated protocol, Part A integrated protocol remained unchanged, except for two administrative changes.
20 October 2015	Amendment 8: The amendment introduced changes to the Part B integrated protocol. The Part A integrated protocol remained unchanged.
18 July 2016	Amendment 9: following modifications applicable to study Part A: Enhanced monitoring of respiratory symptoms. Added monitoring guidelines for opportunistic infection prophylaxis.
11 April 2017	Amendment 10: following modifications applicable to study Part A: Extended the possibility to collect tumor assessment data for beyond 3 years. Identified a new Sponsor's Medical Expert.
21 November 2017	Amendment 11: Replacement of 80 mg vials with 60 mg vials.
31 January 2019	Amendment 13: Extend the study from 3 to 4 years after the last patient started study treatment.
02 March 2022	Amendment 14: Extend the study up to 4 years after the last patient has completed study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported