Clinical trial results:
PHASE 1B OPEN-LABEL STUDY OF THE SAFETY AND CLINICAL ACTIVITY OF CRIZOTINIB (PF-02341066) IN TUMORS WITH GENETIC EVENTS INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) GENE LOCUS

Summary

EudraCT number	2010-022978-14
Trial protocol	IT Outside EU/EEA
Global end of trial date	07 September 2023

Results information

Result version number	v1 (current)
This version publication date	15 March 2024
First version publication date	15 March 2024

Trial information

Trial identification

Sponsor protocol code	A8081013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01121588
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States,
Public contact	Pfizer ClinicalTrials.gov Call Center , Pfizer, Inc. , +1 18007181021,
Scientific contact	Pfizer ClinicalTrials.gov Call Center , Pfizer, Inc. , +1 18007181021,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001493-PIP03-18
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2023
Global end of trial reached?	Yes
Global end of trial date	07 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 1 trial evaluating the safety and efficacy of crizotinib in patients with tumors except non-small cell lung cancer that are positive for ALK.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	44
EEA total number of subjects	12

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	35
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 44 Anaplastic lymphoma kinase (ALK) genetic event positive subjects were enrolled into the study: 17 with anaplastic large cell lymphoma (ALCL), 9 with inflammatory myofibroblastic tumors (IMT), and 18 with other tumors (ALK-positive malignancies excluding nonsmall cell lung cancer).

Pre-assignment

Screening details:

A total of 44 Anaplastic lymphoma kinase (ALK) genetic event positive subjects were enrolled into the study: 17 with anaplastic large cell lymphoma (ALCL), 9 with inflammatory myofibroblastic tumors (IMT), and 18 with other tumors (ALK-positive malignancies excluding nonsmall cell lung cancer). All subjects discontinued study.

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	Anaplastic Large Cell Lymphoma (ALCL)

Arm description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods.

Arm title	Inflammatory Myofibroblastic Tumors (IMT)

Arm description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles

were defined in 21 day periods.

Arm title	Other Tumors

Arm description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods.

Number of subjects in period 1	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors
Started	17	9	18
Completed	0	0	0
Not completed	17	9	18
Adverse event, serious fatal	5	3	13
Non-Specified Reasons	9	4	2
Subject Refused Further Followup	2	-	2
Study Terminated by Sponsor	1	1	-
Lost to follow-up	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Anaplastic Large Cell Lymphoma (ALCL)

Reporting group description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group title	Inflammatory Myofibroblastic Tumors (IMT)

Reporting group description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group title	Other Tumors

Reporting group description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors
Number of subjects	17	9	18
Age Categorical Units: Subjects			
<18 years	3	2	0
Between 18 and 65 years	14	6	15
>=65 years	0	1	3
Age Continuous Units: Years			
median	25.0	32.0	49.0
full range (min-max)	15.0 to 37.0	16.0 to 73.0	18.0 to 73.0
Sex: Female, Male Units: Subjects			
Overall population excluding pediatric|Female	4	3	10
Pediatric Population|Female	1	1	0
Overall population excluding pediatric|Male	10	4	8
Pediatric Population|Male	2	1	0
Race/Ethnicity, Customized Units: Subjects			
White (including 1 pediatric subject with ALCL)	12	4	7
Black	0	0	0
Asian (including 2 ALCL and 2 IMT pediatric)	5	5	11

Age Continuous			
Units: Years			
median	25.0	32.0	49.0
full range (min-max)	15.0 to 37.0	16.0 to 73.0	18.0 to 73.0

Reporting group values	Total		
Number of subjects	44		
Age Categorical			
Units: Subjects			
<18 years	5		
Between 18 and 65 years	35		
>=65 years	4		
Age Continuous			
Units: Years			
median			
full range (min-max)	-		
Sex: Female, Male			
Units: Subjects			
Overall population excluding pediatric|Female	17		
Pediatric Population|Female	2		
Overall population excluding pediatric|Male	22		
Pediatric Population|Male	3		
Race/Ethnicity, Customized			
Units: Subjects			
White (including 1 pediatric subject with ALCL)	23		
Black	0		
Asian (including 2 ALCL and 2 IMT pediatric)	21		
Age Continuous			
Units: Years			
median			
full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Anaplastic Large Cell Lymphoma (ALCL)

Reporting group description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group title	Inflammatory Myofibroblastic Tumors (IMT)

Reporting group description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group title	Other Tumors

Reporting group description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg twice daily (BID) was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Primary: Number of Subjects With All-Causality Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With All-Causality Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant who received study treatment without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes: death, initial or prolonged inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization of prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5= death related to AE.

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

Notes:

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

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	9	18	
Units: Subjects				

AEs	17	9	17	
SAEs	8	4	7	
Maximum Grade 3 or 4 AEs	13	7	8	
Maximum Grade 5 AEs	2	0	4	
AEs resulting in study trt d/c (subject continued)	1	0	3	
AEs resulting in dose reduction	4	1	3	
AEs resulting in temporary d/c of study trt	8	6	10	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With All-Causality TEAEs in the Pediatric Population

End point title	Number of Subjects With All-Causality TEAEs in the Pediatric Population[2]

End point description:

An AE was any untoward medical occurrence in a participant An AE was any untoward medical occurrence in a participant who received study treatment without regard to possibility of causal relationship. Serious AE was an AE resulting in death, initial or prolonged inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication.Grades of AEs were defined by NCI CTCAE version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization of prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5=death related to AE.

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 342 weeks)

Notes:

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

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	0[3]	
Units: Subjects				
AEs	3	2		
SAEs	2	1		
Maximum Grade 3 or 4 AEs	3	2		
Maximum Grade 5 AEs	0	0		
AEs resulting in study trt d/c (subject continued)	0	0		
AEs resulting in dose reduction	1	0		
AEs resulting in temporary d/c of study trt	2	2		

Notes:

[3] - There was 0 pediatric subject in other tumors group

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Related TEAEs

End point title	Number of Subjects With Treatment-Related TEAEs[4]

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a participant who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by NCI CTCAE version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization of prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5=death related to AE.

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

Notes:

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

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	9	18	
Units: Subjects				
AEs	16	8	15	
SAEs	5	3	2	
Maximum Grade 3 or 4 AEs	11	5	6	
Maximum Grade 5 AEs	0	0	2	
AEs resulting in study trt d/c (subject continued)	0	0	2	
AEs resulting in doser reduction	4	1	3	
AEs resulting in temporary d/c of study trt	6	4	6	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Related TEAEs in the Pediatric

Population

End point title	Number of Subjects With Treatment-Related TEAEs in the Pediatric Population[5]

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a participant who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsened in severity after the first dose of study medication. Grades of AEs were defined by NCI CTCAE version 4.03. Grade 3=severe or medically significant but not immediately life-threatening, hospitalization of prolongation of hospitalization indicated; disabling limiting self-care ADL; Grade 4=events with life-threatening consequences, urgent intervention indicated; Grade 5=death related to AE.

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 342 weeks)

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: No statistical analysis was planned.

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	0[6]	
Units: Subjects				
AEs	3	2		
SAEs	2	1		
Maximum Grade 3 or 4 AEs	2	1		
Maximum Grade 5 AEs	0	0		
AEs resulting in study trt d/c (subject continued)	0	0		
AEs resulting in dose reduction	1	0		
AEs resulting in temporary d/c of study trt	1	1		

Notes:

[6] - Zero pediatric subject in other tumors group was reported for this endpoint

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Test Results Shifted From Grade <=2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries)

End point title	Number of Subjects With Laboratory Test Results Shifted From Grade <=2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries)[7]

End point description:

Baseline assessment was defined as the last assessment performed on or prior to the date of the first dose of study treatment. Both hematology and chemisty laboratory assessments were analyzed. Grades of severity were defined by CTCAE v4.0. Grade 2 = moderate adverse event; Grade 3= severe adverse event; Grade 4 = life-threatening consequences; urgent intervention indicated.

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

Notes:

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

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	9	16	
Units: Subjects				
Anemia	1	0	5	
Hemoglobin increased	0	0	0	
Lymphocyte count decreased	1	1	4	
Lymphocyte count increased	0	0	0	
Neutrophil count decreased	8	3	1	
Platelet count decreased	0	0	0	
White blood cell decreased	3	0	1	
Alanine aminotransferase increased	2	1	2	
Alkaline phosphatase increased	0	0	0	
Aspartate aminotransferase increased	4	0	1	
Blood bilirubin increased	0	0	1	
Creatinine increased	0	0	0	
Hypercalcemia	0	0	0	
Hyperglycemia	0	0	0	
Hyperkalemia	2	0	0	
Hypermagnesemia	0	0	1	
Hypernatremia	0	0	0	
Hypoalbuminemia	0	0	2	
Hypocalcemia	0	0	0	
Hypoglycemia	2	0	0	
Hypokalemia	0	0	2	
Hypomagnesemia	0	0	0	
Hyponatremia	0	0	2	
Hypophosphatemia	3	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Test Results Shifted From Grade <=2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries) in the Pediatric Population

End point title	Number of Subjects With Laboratory Test Results Shifted From Grade <=2 At Baseline to Grade 3 or 4 Postbaseline (Hematology and Chemistries) in the Pediatric Population[8]

End point description:

Baseline assessment was defined as the last assessment performed on or prior to the date of the first

dose of study treatment. Both hematology and chemisty laboratory assessments were analyzed. Grades of severity were defined by CTCAE v4.0. Grade 2 = moderate adverse event; Grade 3= severe adverse event; Grade 4 = life-threatening consequences; urgent intervention indicated. Unplanned laboratory test results were also included.

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 342 weeks)

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: No statistical analysis was planned.

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	0[9]	
Units: Subjects				
Anemia	0	0		
Hemoglobin increased	0	0		
Lymphocyte count decreased	1	0		
Lymphocyte count increased	0	0		
Neutrophil count decreased	2	1		
Platelet count decreased	0	0		
White blood cell decreased	2	0		
Alanine aminotransferase increased	0	0		
Alkaline phosphatase increased	0	0		
Aspartate aminotransferase increased	1	0		
Blood bilirubin increased	0	0		
Creatinine increased	0	0		
Hypercalcemia	0	0		
Hyperglycemia	0	0		
Hyperkalemia	0	0		
Hypermagnesemia	0	0		
Hypernatremia	0	0		
Hypoalbuminemia	0	0		
Hypocalcemia	0	0		
Hypoglycemia	1	0		
Hypokalemia	0	0		
Hypomagnesemia	0	0		
Hyponatremia	0	0		
Hypophosphatemia	1	0		

Notes:

[9] - There was 0 pediatric subject in other tumors group

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) - Percentage of Subjects With Objective Response

End point title	Objective Response Rate (ORR) - Percentage of Subjects With

	Objective Response[10]

End point description:

Percentage of participants with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) (1.1) as determined by the investigators. CR = disappearance of all target lesions. PR = greater than equal to (>=) 30% decrease in sum of target lesions taking as reference baseline sum diameters. ORR based on Cheson criteria was defined similarly however, confirmation of response was not required. If participant had tumor response assessed only by RECIST or Cheson, then ORR was based on the single result. If tumor response was assessed by both RECIST and Cheson, then ORR was reported based on tumor response by Cheson criteria unless the Cheson has indeterminate result, in which case the RECIST result was reported. Participant(s) who did not have tumor assessment results from either RECIST 1.1 or Cheson criteria reported at baseline were to be excluded from the analysis.

End point type	Primary

End point timeframe:

From the date of first dose of study medication to the date of the first documentation of objective tumor progression or death on treatment due to any cause, whichever occured first (maximum 374 weeks)

Notes:

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

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	9	18	
Units: Percentage of subjects				
number (confidence interval 95%)	56.3 (33.2 to 76.9)	66.7 (35.4 to 87.9)	16.7 (5.8 to 39.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Based on Investigator Assessement

End point title	Progression-Free Survival (PFS) Based on Investigator Assessement

End point description:

PFS was defined as the time from the date of first dose of study medication to the date of the first documentation of objective tumor progression (at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study [this includes the baseline sum if that is the smallest on study]). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression) or death on treatment due to any cause, whichever occured first. If tumor progression data included more than 1 date, the first date was used. The median PFS was estimated using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From the date of first dose of study medication to the date of the first documentation of objective tumor progression or death on treatment due to any cause, whichever occurs first (maximum 444 weeks)

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17[11]	9[12]	18	
Units: Months				
median (confidence interval 95%)	99999 (2.1 to 99999)	99999 (11.1 to 99999)	1.4 (1.1 to 4.9)	

Notes:

[11] - Median PFD and upper limit of CI not estimable due to insufficient number of subjects with event.

[12] - Median PFD and upper limit of CI not estimable due to insufficient number of subjects with event.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Surviving at 6 Months and 1 Year

End point title	Percentage of Participants Surviving at 6 Months and 1 Year

End point description:

The probability of survival at 6 months and 1 year, respectively, after the date of the first dose based on the Kaplan-Meier estimate.

End point type	Secondary

End point timeframe:

At 6 months and 1 year after first dose

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	9	18	
Units: Percentage of subjects				
number (confidence interval 95%)				
6 Months	76.5 (48.8 to 90.4)	100.0 (100.0 to 100.0)	52.9 (27.6 to 73.0)	
1 Year	70.6 (43.1 to 86.6)	100.0 (100.0 to 100.0)	52.9 (27.6 to 73.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from the date of first dose of study medication to the date of death due to any cause. OS (in months) was calculated as (date of death − date of first dose +1)/30.42. For subjects still alive at the time of the analysis, for those who were lost to follow-up, and those who withdrew consent for additional follow up, the OS was censored on the last date that participants were known to be alive. Subjects lacking data beyond the first dose had their OS censored at the date of first dose. The median

OS was estimated using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From the first dose of study treatment to the date of death due to any cause (maximum 444 weeks)

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17[13]	9[14]	18	
Units: Months				
median (confidence interval 95%)	99999 (7.5 to 99999)	99999 (32.1 to 99999)	12.6 (2.2 to 27.0)	

Notes:

[13] - Median OS and upper limit of CI not estimable due to insufficient number of subjects with event.

[14] - Median OS and upper limit of CI not estimable due to insufficient number of subjects with event.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) Based on Investigator Assessement

End point title	Duration of Response (DR) Based on Investigator Assessement

End point description:

DR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. CR: disappearance of all lesions; any pathological lymph nodes (target lesions [TLs]) or non-target lesions (non-TLs) must have reduction in short axis to <10 mm; normalization of tumor marker level for non-TLs; PR: >=30% decrease in sum of diameter of all TLs, taking as reference baseline sum of diameters; DR (in weeks) was calculated as (first date of PD or death − first date of CR or PR +1)/7. The median DR was estimated using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first (maximum 374 weeks)

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[15]	6[16]	3[17]	
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (30.1 to 9999)	9999 (16.1 to 9999)	

Notes:

[15] - This is showing DR for the patients without subsequent progression or death

[16] - This is showing DR for the patients without subsequent progression or death

[17] - This is showing DR for the patients without subsequent progression or death

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Pre-dose Concentration (Ctrough) for Crizotinib on Day 1 of Cycles 2, 3 and 5

End point title	Steady-State Pre-dose Concentration (Ctrough) for Crizotinib on Day 1 of Cycles 2, 3 and 5

End point description:

Ctrough is defined as the drug concentration observed at the last planned timepoint prior to dosing. Steady state is defined as the subject receiving at least 90% of Crizotinib 500 mg daily dosing 14 days prior to the PK sample collection.

End point type	Secondary

End point timeframe:

Predose within 1.2 hours before dosing on Day 1 of Cycles 2, 3 and 5

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	8	12	
Units: nanogram per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	270 (± 46.2)	266 (± 42.0)	233 (± 101)	
Cycle 3 Day 1	316 (± 33.4)	179 (± 92.1)	187 (± 224)	
Cycle 5 Day 1	244 (± 80.0)	257 (± 35.1)	347 (± 63.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Ctrough for PF-06260182 on Day 1 of Cycles 2, 3 and 5

End point title	Steady-State Ctrough for PF-06260182 on Day 1 of Cycles 2, 3 and 5

End point description:

Ctrough is defined as the drug concentration observed at the last planned timepoint prior to dosing. Steady state is defined as the subject receiving at least 90% of Crizotinib 500 mg daily dosing 14 days prior to the PK sample collection.

End point type	Secondary

End point timeframe:

Predose within 1.2 hours before dosing on Day 1 of Cycles 2, 3 and 5

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	8	12	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	79.7 (± 64.6)	68.2 (± 56.4)	54.6 (± 123)	
Cycle 3 Day 1	85.4 (± 88.2)	41.7 (± 147)	50.5 (± 566)	
Cycle 5 Day 1	81.7 (± 96.8)	71.9 (± 48.2)	91.7 (± 68.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough Ratios of PF-06260182 to Crizotinib on Day 1 of Cycles 2, 3 and 5

End point title	Ctrough Ratios of PF-06260182 to Crizotinib on Day 1 of Cycles 2, 3 and 5

End point description:

Ctrough is defined as the drug concentration observed at the last planned timepoint prior to dosing. Steady state is defined as the participant receiving at least 90% of Crizotinib 500 mg daily dosing 14 days prior to the PK sample collection. The ratio is calculated as: (PF-06260182 concentration/464.33)/(Crizotinib concentration/450.34), where 464.33 is molecular weight for PF-06260182 and 450.33 is molecular weight for Crizotinib.

End point type	Secondary

End point timeframe:

Predose within 1.2 hours before dosing on Day 1 of Cycles 2, 3 and 5

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	8	12	
Units: ratio				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	0.323 (± 15.2)	0.249 (± 25.0)	0.190 (± 32.7)	
Cycle 3 Day 1	0.314 (± 26.0)	0.226 (± 41.4)	0.126 (± 108)	
Cycle 5 Day 1	0.326 (± 28.3)	0.270 (± 27.7)	0.243 (± 28.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With ALK Genetic Events

End point title	Number of Subjects With ALK Genetic Events

End point description:

Planned analysis (molecular profiling results including ALK fusion/translocation, mutations, amplification and overexpression) was not performed due to insufficient samples.

End point type	Secondary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[18]	0[19]	0[20]	
Units: Subjects				

Notes:

[18] - The analysis was not performed due to insufficient samples.

[19] - The analysis was not performed due to insufficient samples.

[20] - The analysis was not performed due to insufficient samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Phosphorylation Status of ALK in the Tumor Samples From Surgery or Biopsy Pre and Post Treatment

End point title	Phosphorylation Status of ALK in the Tumor Samples From Surgery or Biopsy Pre and Post Treatment

End point description:

Tumor sample was planned to be provided to the designated central laboratory for retrospective confirmation of ALK genetic event by a Pfizer designated central laboratory. The molecular profiling results were planned to include ALK fusion/translocation, mutations, amplification and overexpression. The analysis was not performed due to insufficient samples.

End point type	Secondary

End point timeframe:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum 444 weeks)

End point values	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[21]	0[22]	0[23]	
Units: Subjects				

Notes:

[21] - The analysis was not performed due to insufficient samples.

[22] - The analysis was not performed due to insufficient samples.

[23] - The analysis was not performed due to insufficient samples.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study treatment up to 28 days after the last dose of study treatment (maximum duration between first and last dose: 604.1 weeks)

Adverse event reporting additional description:

Same event may appear as non-SAE and SAE; however, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Anaplastic Large Cell Lymphoma (ALCL)

Reporting group description:

In ALK genetic event positive subjects with ALCL, crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group title	Inflammatory Myofibroblastic Tumors (IMT)

Reporting group description:

In ALK genetic event positive subjects with IMT, crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Subjects could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Reporting group title	Other Tumors

Reporting group description:

In ALK genetic event positive participants with other tumors (excluding nonsmall cell lung cancer), crizotinib 250 mg BID was administered orally at approximately the same time each day on a continuous daily dosing schedule. Crizotinib was allowed to be taken without regard to meals. Cycles were defined in 21 day periods. Participants could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Serious adverse events	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)	4 / 9 (44.44%)	7 / 18 (38.89%)
number of deaths (all causes)	5	3	13
number of deaths resulting from adverse events	3	0	4
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (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

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 17 (17.65%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Myocardial ischaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Eyelid ptosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (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
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Faecaloma			

subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (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
Intestinal obstruction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Neurogenic bladder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (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
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Anaplastic Large Cell Lymphoma (ALCL)	Inflammatory Myofibroblastic Tumors (IMT)	Other Tumors
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)	9 / 9 (100.00%)	17 / 18 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tumour associated fever			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cancer pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Varicose vein			

subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Mole excision			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	7 / 17 (41.18%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	10	0	2
Chest discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Chest pain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Cyst			

subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	4 / 17 (23.53%)	1 / 9 (11.11%)	5 / 18 (27.78%)
occurrences (all)	5	1	9
Gait disturbance			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	5 / 17 (29.41%)	3 / 9 (33.33%)	6 / 18 (33.33%)
occurrences (all)	28	6	10
Pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Peripheral swelling			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	8	0	0
Pyrexia			
subjects affected / exposed	10 / 17 (58.82%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	18	1	2
Swelling face			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Erectile dysfunction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Intermenstrual bleeding			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vaginal discharge			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 17 (17.65%)	1 / 9 (11.11%)	4 / 18 (22.22%)
occurrences (all)	4	5	6
Atelectasis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	7 / 17 (41.18%)	1 / 9 (11.11%)	4 / 18 (22.22%)
occurrences (all)	9	1	4
Pharyngeal erythema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Paranasal cyst			

subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	2	1	3
Nasal congestion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tonsillar hypertrophy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	5	3	1
Respiratory tract congestion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pulmonary hypertension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Productive cough			

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	3	2
Aggression			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	3
Libido decreased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Delirium			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Investigations			
Blood glucose decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	9 / 17 (52.94%)	4 / 9 (44.44%)	5 / 18 (27.78%)
occurrences (all)	53	26	12
Amylase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	10 / 17 (58.82%)	4 / 9 (44.44%)	6 / 18 (33.33%)
occurrences (all)	34	20	12
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 9 (22.22%)	1 / 18 (5.56%)
occurrences (all)	0	2	4
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 17 (23.53%)	2 / 9 (22.22%)	0 / 18 (0.00%)
occurrences (all)	38	3	0
Blood creatinine increased			
subjects affected / exposed	3 / 17 (17.65%)	2 / 9 (22.22%)	1 / 18 (5.56%)
occurrences (all)	5	2	1
Blood folate decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood testosterone decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood uric acid increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Globulins decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	9	0	0
Lipase increased			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Neutrophil count decreased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	9	0	0
Platelet count decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Weight decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	6	2	0
White blood cell count decreased			
subjects affected / exposed	5 / 17 (29.41%)	2 / 9 (22.22%)	1 / 18 (5.56%)
occurrences (all)	61	3	6

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Contusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Exposure during pregnancy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Paternal exposure during pregnancy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pelvic fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Wrist fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Injury			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			

Gilbert's syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	6 / 17 (35.29%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	7	1	2
Dysgeusia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dysaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Amnesia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Ageusia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Petit mal epilepsy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Visual perseveration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Taste disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	3	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 9 (22.22%)	6 / 18 (33.33%)
occurrences (all)	8	6	7
Lymph node pain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Lymphoid tissue hyperplasia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	3 / 17 (17.65%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	33	8	16
Myelosuppression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Neutropenia			
subjects affected / exposed	7 / 17 (41.18%)	4 / 9 (44.44%)	3 / 18 (16.67%)
occurrences (all)	75	28	9

Thrombocytopenia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	2
Leukopenia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 9 (22.22%)	2 / 18 (11.11%)
occurrences (all)	4	4	11
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Otorrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blindness unilateral			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Diplopia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Photopsia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	0
Vision blurred			

subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Visual impairment			
subjects affected / exposed	8 / 17 (47.06%)	4 / 9 (44.44%)	5 / 18 (27.78%)
occurrences (all)	8	4	7
Vitreous floaters			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Abdominal discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	5 / 17 (29.41%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	7	3	2
Abdominal pain lower			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	6 / 17 (35.29%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	9	0	3
Abdominal tenderness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Constipation			
subjects affected / exposed	5 / 17 (29.41%)	1 / 9 (11.11%)	3 / 18 (16.67%)
occurrences (all)	7	1	3
Diarrhoea			
subjects affected / exposed	11 / 17 (64.71%)	3 / 9 (33.33%)	6 / 18 (33.33%)
occurrences (all)	26	3	9
Dyspepsia			
subjects affected / exposed	4 / 17 (23.53%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	6	1	0
Enteritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Gastric ulcer			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Gingival bleeding			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hiatus hernia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	6 / 17 (35.29%)	5 / 9 (55.56%)	7 / 18 (38.89%)
occurrences (all)	16	9	14
Odynophagia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0

Proctitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	10 / 17 (58.82%)	3 / 9 (33.33%)	6 / 18 (33.33%)
occurrences (all)	29	8	11
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 17 (23.53%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	7	1	0
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Cholangitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cholelithiasis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Acne			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Dermatitis acneiform			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Skin lesion			

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Erythema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hair disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hair growth abnormal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hand dermatitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hirsutism			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	3 / 17 (17.65%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	4	1	0
Purpura			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pruritus			

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Onychomadesis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Mechanical urticaria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin mass			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Urinary incontinence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Muscle disorder			

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Joint effusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Costochondritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	4 / 17 (23.53%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Muscle fatigue			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pseudarthrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pain in jaw			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
Muscular weakness			

subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			
Klebsiella infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eyelid folliculitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Genital herpes			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Infected cyst			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	5 / 17 (29.41%)	1 / 9 (11.11%)	1 / 18 (5.56%)
occurrences (all)	6	1	2
Mucosal infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Oesophageal candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Oral herpes			
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Otitis externa			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Pelvic infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 17 (5.88%)	2 / 9 (22.22%)	1 / 18 (5.56%)
occurrences (all)	4	3	1
Sinusitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 17 (29.41%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	15	14	0
Vaginal infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Nasopharyngitis			
subjects affected / exposed	6 / 17 (35.29%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	17	1	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 17 (17.65%)	3 / 9 (33.33%)	4 / 18 (22.22%)
occurrences (all)	4	3	4
Hypoproteinaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Hypophosphataemia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 9 (22.22%)	1 / 18 (5.56%)
occurrences (all)	11	8	1
Hyponatraemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	3 / 18 (16.67%)
occurrences (all)	1	0	4
Hypocalcaemia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	2 / 18 (11.11%)
occurrences (all)	4	2	3
Hypoalbuminaemia			
subjects affected / exposed	1 / 17 (5.88%)	3 / 9 (33.33%)	3 / 18 (16.67%)
occurrences (all)	1	17	6
Hyperuricaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2010	Additional safety monitoring language for pneumonitis; inclusion/exclusion criteria updated
17 December 2010	Removal of 150mg capsule strength; further clarification given on Dose Modifications for drug related toxicities; introduction of SAE reporting requirements for Drug Induced Liver Injury; inclusion/exclusion criteria updated.
17 July 2012	1. Protocol summary: New safety language included; 2. Table 1. Schedual of Activities: New safety monitoring added (urinalysis), changes to study conduct (decrease in visit frequency, addition of bone marrow biopsy and/or aspirates for lymphoma patients); 3. Protocl sections 2 and 3: Changes the analysis tool for evaluating disease response in lymphoma patients and thus changes the conduct of the trial; 4. Protocl section 4: Conduct of study altered by shortened chemotherapy washout period and requirement for measurable disease at study entry. New safety language added to minimize risk of exposure in utero; 5. Protocol section 5: Specification of acceptable contraceptive measures constitutes change in study conduct, new safety language added; 6. Protocol section 7: Addition of PET and bone marrow biopsy constitute change in study conduct; 8. Protocol section 9: New efficacy descriptors constitute change in study conduct; 10, References and addition of new disease response criteria constitutes a change in study conduct was added in appendix 4.
19 April 2013	Non-substantia changes were maded for updating the protocol with new text as required by the new protocol template.
13 August 2015	1. Protocol summary: A reduced schedule of activities were updated, 2. Protocol section 4: new requirements about contraception and an updated definition of females of non-child-bearing potential have been added; 3. protocol section 5: Additional details about the requirements for drug storage condition, concomitant medications and patient management regarding bradycardia, change in the dosing guidance regarding pneumonitis, and additional guidance for renal cyst were added; 4. Protocol section 12: details on the assent and de identification procedures were added; 5. protocol section 15: clarifications to the Pfizer public disclosure procedure have been provided. 6. protocol section appedix 5: the schedule of activities has been reduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported