Clinical trial results:
A Multi-Center, Open-Label, Compassionate Use Extension Study of Ublituximab (TG-1101) in Combination with Umbralisib (TGR-1202) for Patients Previously Enrolled in Protocol UTX-TGR-304

Summary

EudraCT number	2016-004339-19
Trial protocol	PL ES GB IT
Global end of trial date	11 July 2022

Results information

Result version number	v1 (current)
This version publication date	27 July 2023
First version publication date	27 July 2023

Trial information

Trial identification

Sponsor protocol code	UTX-TGR-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02656303
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TG Therapeutics, Inc.
Sponsor organisation address	2 Gansevoort Street, 9th Floor, New York, United States, 10014
Public contact	Clinical Support Team, TG Therapeutics, 1 877-575-8489, Clinicalsupport@tgtxinc.com
Scientific contact	Clinical Support Team, TG Therapeutics, 1 877-575-8489, Clinicalsupport@tgtxinc.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	11 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to provide the opportunity to the subjects who progressed on treatment arm previously in the study UTX-TGR-304 (2015-005758-36) to receive ublituximab (TG-1101) treatment in combination with umbralisib (TGR-1202).

Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all ICH GCP Guidelines. The Investigator or his/her representative explained the nature of the study to the subject or his/her legally authorized representative and answered all questions regarding the study. Subjects and/or their legally authorized representative were informed that their participation was voluntary. Subjects or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center. Investigative sites were instructed to obtain written informed consent before the subject was enrolled in the study and document the date the written consent was obtained. The authorized person obtaining the informed consent was also instructed to sign the ICF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2017
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	Poland: 43
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 68
Worldwide total number of subjects	116
EEA total number of subjects	47

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)	47
From 65 to 84 years	67
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 116 subjects took part across 50 investigative sites in the United States, United Kingdom, Italy, and Poland from 03 January 2017 to 28 June 2022.

Pre-assignment

Screening details:

Subjects previously enrolled in the parent study UTX-TGR-304 (2015-005758-36) were enrolled in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Parent Study Arm B

Arm description:

Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 milligrams (mg), intravenously (IV), on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Arm type	Experimental
Investigational medicinal product name	Ublituximab
Investigational medicinal product code	
Other name	TG-1101
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ublituximab 150 mg was administered as an IV on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter.

Investigational medicinal product name	Umbralisib
Investigational medicinal product code	
Other name	TGR-1202
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Umbralisib 800 mg was administered orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Arm title	Parent Study Arm C

Arm description:

Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Arm type	Experimental

Investigational medicinal product name	Ublituximab
Investigational medicinal product code	
Other name	TG-1101
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ublituximab 900 mg was administered as an IV on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter.

Investigational medicinal product name	Umbralisib
Investigational medicinal product code	
Other name	TGR-1202
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Umbralisib 800 mg was administered orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Arm title	Parent Study Arm D

Arm description:

Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Arm type	Experimental
Investigational medicinal product name	Ublituximab
Investigational medicinal product code	
Other name	TG-1101
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ublituximab 150 mg was administered as an IV on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter.

Investigational medicinal product name	Umbralisib
Investigational medicinal product code	
Other name	TGR-1202
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Umbralisib 800 mg was administered, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Number of subjects in period 1	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D
Started	67	31	18
Completed	0	0	0
Not completed	67	31	18
Non-compliance with study	1	1	-
Death	12	4	1

Initiation of non-protocol intervention	1	-	-
Adverse event	3	2	-
Investigator decision	2	1	-
Study terminated by sponsor	20	7	5
Progressive disease	25	14	10
Reason not specified	1	1	2
Lack of efficacy	1	-	-
Withdrawal of consent by subject	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Parent Study Arm B
Reporting group description:	
Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 milligrams (mg), intravenously (IV), on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.	
Reporting group title	Parent Study Arm C
Reporting group description:	
Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.	
Reporting group title	Parent Study Arm D
Reporting group description:	
Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.	

Reporting group values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D
Number of subjects	67	31	18
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	65.6	66.7	65.7
standard deviation	± 8.18	± 9.41	± 8.79
Gender categorical Units: Subjects			
Female	19	5	5
Male	48	26	13
Race Units: Subjects			
White	65	30	15
Black or African American	2	0	1
Other	0	0	2
Not Reported	0	1	0

Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	66	30	16
Unknown or Not Reported	0	1	1

Reporting group values	Total		
Number of subjects	116		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	29		
Male	87		
Race Units: Subjects			
White	110		
Black or African American	3		
Other	2		
Not Reported	1		
Ethnicity Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	112		
Unknown or Not Reported	2		

End points

End points reporting groups

Reporting group title	Parent Study Arm B

Reporting group description:

Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 milligrams (mg), intravenously (IV), on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Reporting group title	Parent Study Arm C

Reporting group description:

Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Reporting group title	Parent Study Arm D

Reporting group description:

Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Primary: Overall Response Rate (ORR) as Per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Criteria

End point title	Overall Response Rate (ORR) as Per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Criteria[1]

End point description:

ORR was defined as sum of subjects with partial response (PR) and complete response (CR). CR: No evidence of new disease; Absolute lymphocyte count (ALC)<4x10^9/litre(L); Regression of all target nodal masses to ≤1.5 centimetres (cm) in longest diameter(LD); Normal spleen, liver size; Regression to normal of all nodal non-target disease and disappearance of all detectable; Non-nodal, non-target disease; Morphologically negative bone marrow; No lymphoid nodules; Absolute neutrophil count (ANC)>1.5x10^9/L, platelets≥100x10^9/L, hemoglobin (Hgb)≥110 gram per litre(g/L). PR: No evidence of new disease; Response in 2 of following if abnormal at baseline: ALC<4x10^9/L or ≥50% decrease from baseline in sum of products (SPD) of target nodal lesions; splenomegaly; hepatomegaly; ≥50% decrease from baseline in CLL marrow infiltrate/B-lymphoid nodules; response in any 1: ANC>1.5x10^9/L, platelets>100x10^9/L, Hgb>110g/L or ≥50% increase over baseline in any of these.

End point type	Primary

End point timeframe:

Up to 76 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

End point values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: subjects				

Notes:

[2] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[3] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[4] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

Statistical analyses

No statistical analyses for this end point

Primary: Complete Response (CR) Rate Per iwCLL Criteria

End point title	Complete Response (CR) Rate Per iwCLL Criteria[5]

End point description:

The CR rate was defined as the percentage of subjects who achieved CR. CR: No evidence of new disease; ALC <4 x 10^9/L; Regression of all target nodal masses to normal size ≤1.5 cm in the LD; Normal spleen and liver size; Regression to normal of all nodal non-target disease and disappearance of all detectable; Non-nodal, non-target disease; Morphologically negative bone marrow; No lymphoid nodules; ANC >1.5 x 10^9/L, platelets ≥100 x 10^9/L, Hgb ≥110 g/L.

End point type	Primary

End point timeframe:

Up to 76 months

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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

End point values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[6]	0[7]	0[8]	
Units: subjects				

Notes:

[6] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[7] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[8] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) Per iwCLL Criteria

End point title	Progression-Free Survival (PFS) Per iwCLL Criteria[9]

End point description:

PFS was defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression (PD) or death from any cause. PD was appearance of new nodes >1.5 cm in the LD and >1.0 in longest perpendicular diameter (LPD), new or recurrent hepatomegaly or splenomegaly, new or reappearance of an unequivocal extra-nodal lesion, ≥50% increase from the nadir in the SPD of target lesions, ≥50% increase in the LD of an individual node or extra-nodal mass, splenic/hepatic enlargement of ≥50% from nadir, unequivocal increase in the size of non-target disease, transformation to a more aggressive histology, decrease in platelet count or Hgb, >50% decrease from the highest on-study platelet count, >20 g/L decrease from the highest on-study Hgb.

End point type	Primary

End point timeframe:

Up to 76 months

Notes:

[9] - 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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

End point values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: months				

Notes:

[10] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[11] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[12] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[13]

End point description:

DOR: Interval from first documentation of CR/PR to first documentation of PD or death from any cause. CR: ALC<4x10^9/L; Regression to normal of target nodal masses,nodal non-target disease,and no detectable non-nodal,non-target disease; Normal spleen,liver size; Morphologically negative bone marrow,No lymphoid nodules;ANC>1.5x10^9/L,Platelets≥100x10^9/L,Hgb≥110 g/L. PR: Response in 2 or more:ALC<4x10^9/L, ≥50% drop from baseline in ALC or SPD of target nodal lesions,Hepatosplenomegaly,≥50% decrease from baseline in CLL marrow infiltrate/B-lymphoid nodules;Response in 1 or more:ANC>1.5x10^9/L,Platelets>100x10^9/L,Hgb>110 g/L or ≥50% increase over baseline in any. PD: Response in 1 or more:new nodes,Hepatosplenomegaly,unequivocal extra-nodal lesion;≥50% increase from nadir in SPD of target lesions or LD of node/extra-nodal mass or Splenic/Hepatic size,Unequivocal increase in non-target disease,More aggressive histology;Drop of >50% in platelets/>20g/L in Hgb from highest on-study count.

End point type	Primary

End point timeframe:

Up to 76 months

Notes:

[13] - 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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

End point values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: months				

Notes:

[14] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[15] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[16] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD) Negativity Rate

End point title	Minimal Residual Disease (MRD) Negativity Rate

End point description:

MRD negativity rate is defined as the percentage of subjects who are MRD negative. If a subject was determined to be MRD negative by peripheral blood, a bone marrow aspirate was obtained to assess MRD in the bone marrow.

End point type	Secondary

End point timeframe:

From Cycle 6 until Cycle 15 (cycle length=28 days) (Up to approximately 76 months)

End point values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: subjects				

Notes:

[17] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[18] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.
[19] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing at Least One Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Subjects Experiencing at Least One Treatment-Emergent Adverse Event (TEAE)

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAE is any AE that occur after first dosing of study medication and through the end of the study or through 30 days after the last dose of study treatment, or is considered treatment-related regardless of the start date of the event, or is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment-related. Safety population included all subjects who were enrolled and received at least one dose of study drug.

End point type	Secondary

End point timeframe:
Up to 78 months

End point values	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	31	18	
Units: subjects	66	30	18	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 78 months

Adverse event reporting additional description:

Safety population included all subjects who were enrolled and received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Parent Study Arm B

Reporting group description:

Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Reporting group title	Parent Study Arm C

Reporting group description:

Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Reporting group title	Parent Study Arm D

Reporting group description:

Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

Serious adverse events	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 67 (53.73%)	13 / 31 (41.94%)	8 / 18 (44.44%)
number of deaths (all causes)	23	9	7
number of deaths resulting from adverse events	9	3	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Lung adenocarcinoma			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
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			
Chest pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Death			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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 / 1	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Pyrexia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Sudden cardiac death			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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 / 1	0 / 0	0 / 0

Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (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
Lung disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Pleural effusion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Blood creatinine increased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Hip fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Infusion related reaction			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Radius fracture			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (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

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Paraparesis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node haemorrhage			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Neutropenia			

subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Cholelithiasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Babesiosis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Bronchitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	4 / 67 (5.97%)	1 / 31 (3.23%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	1 / 5	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 5	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Pneumonia			

subjects affected / exposed	8 / 67 (11.94%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	6 / 13	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	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
Respiratory tract infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Sepsis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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
Hypokalaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Parent Study Arm B	Parent Study Arm C	Parent Study Arm D
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 67 (97.01%)	30 / 31 (96.77%)	17 / 18 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Adenocarcinoma			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Basal cell carcinoma			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Lipoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Malignant melanoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Renal neoplasm			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Squamous cell carcinoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Arteriosclerosis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Deep vein thrombosis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Flushing			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	4	1	1
Hot flush			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Hypertension			
subjects affected / exposed	6 / 67 (8.96%)	3 / 31 (9.68%)	2 / 18 (11.11%)
occurrences (all)	8	10	8
Hypotension			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	3	2	1
Pallor			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Thrombosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Varicose vein			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Surgical and medical procedures			
Pleurodesis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	11 / 67 (16.42%)	4 / 31 (12.90%)	2 / 18 (11.11%)
occurrences (all)	14	11	2
Axillary pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Catheter site erythema			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	13 / 67 (19.40%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	19	3	0
Face oedema			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	23 / 67 (34.33%)	12 / 31 (38.71%)	2 / 18 (11.11%)
occurrences (all)	41	20	2
Feeling abnormal			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Feeling cold			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gait disturbance			

subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Hypothermia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
subjects affected / exposed	14 / 67 (20.90%)	6 / 31 (19.35%)	3 / 18 (16.67%)
occurrences (all)	18	7	7
Peripheral swelling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	14 / 67 (20.90%)	1 / 31 (3.23%)	4 / 18 (22.22%)
occurrences (all)	22	1	4
Secretion discharge			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Swelling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Contrast media allergy			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Hypogammaglobulinaemia			
subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences (all)	3	2	2
Seasonal allergy			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cervical dysplasia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haematospermia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pelvic discomfort			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Prostatomegaly			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Testicular oedema			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Choking			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cough			

subjects affected / exposed	22 / 67 (32.84%)	5 / 31 (16.13%)	3 / 18 (16.67%)
occurrences (all)	32	7	3
Dysphonia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Dyspnoea			
subjects affected / exposed	10 / 67 (14.93%)	4 / 31 (12.90%)	3 / 18 (16.67%)
occurrences (all)	14	5	3
Dyspnoea exertional			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Haemoptysis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypercapnia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypoxia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Increased viscosity of upper respiratory secretion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Lung consolidation			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Lung infiltration			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Lung opacity			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	4 / 67 (5.97%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	4	2	0
Oropharyngeal pain			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Paranasal sinus discomfort			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	2 / 18 (11.11%)
occurrences (all)	3	1	4
Pneumothorax			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	8	3	0
Pulmonary embolism			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pulmonary oedema			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0

Respiratory tract congestion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Respiratory tract inflammation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Respiratory tract irritation			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	5	2	2
Rhinorrhoea			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Sinus congestion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Throat irritation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Throat tightness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tracheomalacia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	4	1	1
Wheezing			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	1	2	1

Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Agitation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	7 / 67 (10.45%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	8	3	0
Confusional state			
subjects affected / exposed	6 / 67 (8.96%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	6	4	0
Delirium			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Hallucination			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	16 / 67 (23.88%)	5 / 31 (16.13%)	3 / 18 (16.67%)
occurrences (all)	19	5	4
Mental status changes			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Mood altered			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Personality change			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Restlessness			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Somatic symptom disorder			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 67 (22.39%)	6 / 31 (19.35%)	3 / 18 (16.67%)
occurrences (all)	25	16	9
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 67 (22.39%)	4 / 31 (12.90%)	2 / 18 (11.11%)
occurrences (all)	24	11	2
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 67 (10.45%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	11	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	3 / 67 (4.48%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Blood creatine increased			
subjects affected / exposed	6 / 67 (8.96%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	10	6	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Blood potassium decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Blood pressure increased			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Blood sodium decreased			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	8	0	0
Blood urea increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Blood urine present			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haematocrit increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	5
Lymphocyte count decreased			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences (all)	0	4	4
Lymphocyte count increased			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
Monocyte percentage decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Neutrophil count decreased			
subjects affected / exposed	3 / 67 (4.48%)	3 / 31 (9.68%)	5 / 18 (27.78%)
occurrences (all)	36	4	13
Neutrophil percentage decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences (all)	11	3	5
Prostatic specific antigen increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Urine output decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	6 / 67 (8.96%)	4 / 31 (12.90%)	2 / 18 (11.11%)
occurrences (all)	7	7	2
Weight increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences (all)	3	6	5
White blood cell count increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 67 (8.96%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	6	3	2
Fall			

subjects affected / exposed	4 / 67 (5.97%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	7	1	0
Fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Incision site pain			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	15 / 67 (22.39%)	5 / 31 (16.13%)	9 / 18 (50.00%)
occurrences (all)	21	7	10
Limb injury			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Muscle strain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Overdose			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Skin wound			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Spinal compression fracture			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Upper limb fracture			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vaccination complication			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Wrist fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Atrial fibrillation			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Atrial flutter			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Bradycardia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cardiac failure chronic			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Myocardial infarction			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Palpitations			

subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tachyarrhythmia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	1	3	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dementia			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Disturbance in attention			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	12 / 67 (17.91%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	18	3	1
Drooling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dysaesthesia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Dysgeusia			
subjects affected / exposed	3 / 67 (4.48%)	4 / 31 (12.90%)	0 / 18 (0.00%)
occurrences (all)	3	7	0
Encephalopathy			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Essential tremor			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Head discomfort			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	10 / 67 (14.93%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	16	2	1
Hyperaesthesia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	2 / 18 (11.11%)
occurrences (all)	5	1	3
Memory impairment			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Myoclonus			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervous system disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Restless legs syndrome			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Seizure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Slow speech			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Syncope			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	8 / 67 (11.94%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	9	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 67 (11.94%)	3 / 31 (9.68%)	1 / 18 (5.56%)
occurrences (all)	18	3	3
Febrile neutropenia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Increased tendency to bruise			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Iron deficiency anaemia			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	7	1	0
Leukocytosis			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Lymphocytosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	17 / 67 (25.37%)	6 / 31 (19.35%)	6 / 18 (33.33%)
occurrences (all)	55	10	10
Thrombocytopenia			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	2 / 18 (11.11%)
occurrences (all)	5	0	3
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Deafness bilateral			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Deafness unilateral			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Ear pain			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hyperacusis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hypoacusis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Inner ear inflammation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Meniere's disease			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Middle ear inflammation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Vertigo			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Vertigo positional			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blepharitis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Chalazion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Dry eye			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Eye irritation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			

subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Ocular hyperaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Visual brightness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	5	3	0
Abdominal pain			
subjects affected / exposed	5 / 67 (7.46%)	5 / 31 (16.13%)	0 / 18 (0.00%)
occurrences (all)	5	7	0
Abdominal pain lower			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	4 / 67 (5.97%)	4 / 31 (12.90%)	1 / 18 (5.56%)
occurrences (all)	4	6	1
Abdominal tenderness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Constipation			
subjects affected / exposed	11 / 67 (16.42%)	4 / 31 (12.90%)	2 / 18 (11.11%)
occurrences (all)	13	6	3

Dental caries			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	35 / 67 (52.24%)	11 / 31 (35.48%)	6 / 18 (33.33%)
occurrences (all)	114	28	10
Diverticulum intestinal			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	9 / 67 (13.43%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences (all)	12	2	2
Dysphagia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Enterovesical fistula			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Faeces soft			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	4 / 67 (5.97%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	4	2	1
Gastric dilatation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Gastric polyps			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 67 (4.48%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Haematochezia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haemoperitoneum			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Haemorrhoids			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hiatus hernia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Large intestine polyp			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	29 / 67 (43.28%)	10 / 31 (32.26%)	5 / 18 (27.78%)
occurrences (all)	47	15	8
Oral pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Paraesthesia oral			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Tongue discomfort			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tongue ulceration			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	11 / 67 (16.42%)	3 / 31 (9.68%)	1 / 18 (5.56%)
occurrences (all)	16	3	1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cholelithiasis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Drug-induced liver injury			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hepatic failure			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypertransaminasaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			

Actinic keratosis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Alopecia areata			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dermal cyst			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	3	7	1
Ecchymosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Hyperhidrosis			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	0	2	0

Ingrowing nail			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Miliaria			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Night sweats			
subjects affected / exposed	7 / 67 (10.45%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	8	2	1
Onychoclasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Photosensitivity reaction			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Precancerous skin lesion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	7 / 67 (10.45%)	4 / 31 (12.90%)	0 / 18 (0.00%)
occurrences (all)	8	4	0
Psoriasis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	6 / 67 (8.96%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	11	2	1
Rash maculo-papular			

subjects affected / exposed	3 / 67 (4.48%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	3	7	0
Rash pruritic			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin erosion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin irritation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	4	2	0
Chromaturia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Chronic kidney disease			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Dysuria			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Micturition urgency			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0

Nocturia			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Pollakiuria			
subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	3	2	0
Polyuria			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Renal colic			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Renal cyst			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Urinary incontinence			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Urinary retention			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Urinary tract pain			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 67 (17.91%)	4 / 31 (12.90%)	2 / 18 (11.11%)
occurrences (all)	20	11	2
Arthritis			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	3
Back pain			
subjects affected / exposed	12 / 67 (17.91%)	2 / 31 (6.45%)	1 / 18 (5.56%)
occurrences (all)	13	5	2
Bone pain			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Costochondritis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	4	1	1
Gouty arthritis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Groin pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Joint effusion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Joint range of motion decreased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	6 / 67 (8.96%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	12	3	0
Muscle tightness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Muscle twitching			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			

subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	2 / 18 (11.11%)
occurrences (all)	5	1	3
Musculoskeletal chest pain			
subjects affected / exposed	5 / 67 (7.46%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	5	1	1
Musculoskeletal pain			
subjects affected / exposed	6 / 67 (8.96%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	6	0	3
Musculoskeletal stiffness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	4 / 67 (5.97%)	4 / 31 (12.90%)	1 / 18 (5.56%)
occurrences (all)	7	4	1
Neck pain			
subjects affected / exposed	4 / 67 (5.97%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	5	1	0
Osteoarthritis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Pain in extremity			
subjects affected / exposed	6 / 67 (8.96%)	1 / 31 (3.23%)	3 / 18 (16.67%)
occurrences (all)	6	1	3
Pain in jaw			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Spinal osteoarthritis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Babesiosis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Body tinea			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	4 / 67 (5.97%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	5	4	0
COVID-19			
subjects affected / exposed	5 / 67 (7.46%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	6	0	1
Campylobacter infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Chronic sinusitis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Clostridium difficile colitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Cystitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	2 / 18 (11.11%)
occurrences (all)	3	1	2
Cytomegalovirus infection reactivation			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Diverticulitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Epididymitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Fungal oesophagitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Gastroenteritis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	3	2	0
Hordeolum			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Laryngitis			

subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Mastoiditis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Mycobacterium avium complex infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Oral candidiasis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Otitis media			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	12 / 67 (17.91%)	1 / 31 (3.23%)	4 / 18 (22.22%)
occurrences (all)	13	1	4
Pseudomonas infection			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	3 / 67 (4.48%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	5	0	1

Rhinitis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Rhinovirus infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Sepsis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	1 / 18 (5.56%)
occurrences (all)	5	1	1
Skin infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Tooth abscess			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	14 / 67 (20.90%)	9 / 31 (29.03%)	4 / 18 (22.22%)
occurrences (all)	21	10	5
Urinary tract infection			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	10	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 67 (14.93%)	1 / 31 (3.23%)	3 / 18 (16.67%)
occurrences (all)	13	4	3
Dehydration			

subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	0 / 18 (0.00%)
occurrences (all)	5	3	0
Food intolerance			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	2 / 18 (11.11%)
occurrences (all)	4	0	6
Hyperkalaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	24	0	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	5 / 67 (7.46%)	3 / 31 (9.68%)	0 / 18 (0.00%)
occurrences (all)	5	5	0
Hypoglycaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	3
Hypokalaemia			
subjects affected / exposed	9 / 67 (13.43%)	4 / 31 (12.90%)	1 / 18 (5.56%)
occurrences (all)	20	4	1
Hypomagnesaemia			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Hyponatraemia			

subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	0 / 18 (0.00%)
occurrences (all)	6	1	0
Hypophosphataemia			
subjects affected / exposed	4 / 67 (5.97%)	2 / 31 (6.45%)	2 / 18 (11.11%)
occurrences (all)	5	4	3
Iron deficiency			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Obesity			
subjects affected / exposed	0 / 67 (0.00%)	0 / 31 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2016	As per amendment 1: 1. All subjects were required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy (previously at investigator discretion). 2. The phrasing of response assessment intervals was revised for clarity from "at Weeks 12, 24, 36, 48, and every 12 weeks thereafter" to "following the completions of cycles 3, 6, 9 12, 15, and 18 and every 3 cycles thereafter". 3. Urine pregnancy test schedule and wording for tumor evaluation were updated in the schedule of assessments and treatment schedule. 4. The shelf life of ublituximab was increased to 36 months from 24 months when stored between +2 C / +8 C to reflect newly available stability data on ublituximab drug product. 5. Included the most recent adverse event information related to ublituximab and umbralisib corresponding to the latest Investigator Brochures.
07 March 2017	As per amendment 2: 1. Inclusion criteria was updated to provide a minimum time on a study arm of 2 cycles and included units (per microlitre) in regard to absolute neutrophil count (ANC) and platelet count. 2. Exclusion criteria was updated to clarify prophylaxis as "anti-pneumocystis pneumonia prophylaxis" and excluded subjects with prior live virus vaccines. 3. Appendix of the protocol (Contraceptive Guidelines and Pregnancy) was updated to delete the word "highly effective" and included follow-up recommendations for subjects entering the study from treatment arm B (obinutuzumab alone) in Study UTX-TGR-304. 4. Frequency of computed tomography (CT) scans for efficacy evaluation was revised to allow scans at every 3 or 6 cycles after Cycle 9 at the discretion of the investigator, to limit exposure to radiation. 5. The 21-day timeframe for signing informed consent was removed. 6. Informed consent was removed from the table of study assessment of the protocol as it was not a 21-day screening procedure.
29 March 2017	As per amendment 3, definition of SAE was updated.
20 October 2017	As per amendment 4: 1. Inclusion Criteria was updated to include: There is no required timeframe to begin treatment on the protocol, however, if other therapies to treat the disease are implemented in the interim, the subject was not eligible to enroll in the study. 2. Exclusion Criteria was updated to clarify the use of anti-pneumocystis pneumonia prophylaxis. 3. Treatment schedule was updated to increase the screening period from 21 to 28 days, included MRD testing for subjects who had a PR and increased the window for scans from +/- 7 days to +/- 14 days. 4. Specified the treatment schema for subjects crossing over from each of the 4 arms in the UTX-TGR-304 protocol 5. Included information regarding a new vial size for ublituximab. 6. Updated with the latest dose delay/modification guidance for ublituximab and umbralisib, included guidance for diarrhea and colitis events 7. Updated to include process of transferring drug from the UTX-TGR-304 protocol, if applicable. 8. Updated to include the most recent adverse event information related to ublituximab and umbralisib corresponding to the latest Investigator Brochures. 9. Removed text: At follow-up time points, the LDs for individual lesions and the SPD of all nodal target lesions will be considered. Because nodal target lesions that have one or both diameters >0 cm and <1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting perpendicular diameters (PPD) will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2 (i.e., if all lymph nodes measure <1.0 cm^2)" to allow for more accurate measurements of nodal target lesions. 10. Updates were made throughout to include umbralisib as the generic name of TGR-1202.

22 January 2019	As per amendment 5: 1. Inclusion Criteria was updated to clarify that subjects with specified ANC and platelet count can be included unless cytopenias were related to bone marrow involvement and allowed subjects with Gilbert's Disease and Autoimmune Hemolytic Anemia. 2. Inclusion Criteria was updated to include the usage of the modified Cockcroft Gault utilizing ideal body mass. 3. Exclusion Criteria added: Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV IgM is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by polymerase chain reaction (PCR). 4. Tumor Evaluations updated as: Evaluations are to be obtained during cycles 3, 6 & 12. Following cycle 12, evaluations should occur at least every 12 cycles; Serum Virology was added to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM at screening and CMV surveillance while subjects were receiving umbralisib in study assessments and treatment schedule. 5. Follow up assessments schedule was added to clarify follow up assessments if a subject comes off study treatment. 6. Treatment plan was updated to clarify pneumocystis jiroveci pneumonia (PJP) and anti-viral prophylaxis language and provided more clear guidelines for timing of pre-medications for ublituximab. 7. Removed requirement for subjects to discontinue study drugs if held for more than 28 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported