Clinical trial results:
A PROSPECTIVE, OPEN-LABEL, MULTICENTRE PHASE-II TRIAL OF IBRUTINIB PLUS VENETOCLAX PLUS OBINUTUZUMAB IN PHYSICALLY FIT (CIRS 6 & NORMAL CREATININE CLEARANCE) OR UNFIT (CIRS >6 & CREATININE CLEARANCE > 50 ML/MIN) PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH TP53 DELETION (17P-) AND/OR MUTATION (CLL2-GIVE-TRIAL OF THE GCLLSG)

Summary

EudraCT number	2015-004606-41
Trial protocol	DE
Global end of trial date	14 June 2022

Results information

Result version number	v1 (current)
This version publication date	01 February 2023
First version publication date	01 February 2023

Trial information

Trial identification

Sponsor protocol code	CLL2-GIVe

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02758665
WHO universal trial number (UTN)	-
Other trial identifiers	BfArM: 4041383

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
Public contact	Stephan Stilgenbauer, University Hospital Ulm, +49 731 500 45538, stephan.stilgenbauer@uniklinik-ulm.de
Scientific contact	Stephan Stilgenbauer, University Hospital Ulm, +49 731 500 45538, stephan.stilgenbauer@uniklinik-ulm.de

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	14 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of the GIVe regimen in patients with TP53 deletion (17p-) and/or mutation and previously untreated CLL requiring treatment.
For this, the CR rate at cycle 15 (d1; final restaging) will be used as primary parameter for efficacy. The CR rate is defined as the proportion of patients having achieved a CR or a CR with incomplete recovery of the bone marrow (CRi) as best response (according to iwCLL criteria) until cycle 15 (d1; final restaging) from start of therapy.
Efficacy of the regimen will be further assessed by evaluation of the proportion of patients free of disease progression (PD-free rate) after 12 cycles of therapy, overall response rate (ORR), minimal residual disease (MRD) and overall survival as well as other time to event endpoints.

Protection of trial subjects:

Safety measures to prevent or to manage known risks associated with CLL, such as infections or cytopenia or known adverse reactions related to any of the IMPs have been included in the protocol. In chapter 8 of the protocol there are sections how to prevent and manage infusion related reactions under obinutuzumab, how to assess and monitor the risk for tumor lysis syndrome. The protocol includes sections with prohibited medication, especially for ibrutinib and known interactions with CYP3A4 inhibitors or inducers. The protocol provides clear guidance for dose modifications and treatment discontinuation.

Background therapy:

Chronic lymphocytic leukemia (CLL) with TP53 deletion (17p-) and/or mutation has a poor prognosis. Different therapeutic strategies have been tested over the last decade such as fludarabine-based regimens, alemtuzumab, bendamustine alone or with rituximab, lenalidomide, or ofatumumab, but all without compelling evidence for success. For example, with the FCR regimen as the standard 1st line treatment for fit CLL patients, only 5% (1 of 22) of patients with 17p deletion had a complete response (CR) and 40% of patients were free of disease progression at 12 months in the CLL8 trial (Hallek et al., 2010, Stilgenbauer et al., 2014). New agents like Bruton’s Tyrosin Kinase (BTK) inhibitors such as ibrutinib have shown promising results in patients with relapsed or refractory CLL, however, outcome of CLL patients with 17p deletion is inferior to other subgroups (Byrd et al., 2015).
The CLL11 trial revealed an impressive improvement in efficacy with GA-101 (obinutuzumab) as compared to rituximab when combined with chlorambucil (Goede et al., 2014). Moreover, the BCL2 antagonist venetoclax (previously GDC-0199/ABT-199), tested as a single agent in relapsed / refractory CLL patients, showed striking activity with tumor lysis syndrome as dose limiting toxicity (Seymour et al., 2013; Souers et al., 2015; Roberts et al., 2016; Stilgenbauer et al., 2016).
Consequently, the current trial will test a combination regimen consisting of obinutuzumab, ibrutinib and venetoclax (the “GIVe” regimen) as first line treatment in CLL patients with TP53 deletion (17p-) and/or mutation with the aim to demonstrate efficacy in this population at highest unmet medical need.

Evidence for comparator:

not applicable

Actual start date of recruitment	01 September 2016
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	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	26
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 41 patients with high-risk CLL were enrolled between September 2016 and August 2018 from sites in Germany.

Pre-assignment

Screening details:

Eligible patients were aged ≥18 years with previously untreated CLL and del(17p) and/or TP53 mutation requiring treatment, diagnosed according to the International Workshop on CLL (iwCLL) criteria. Diagnosis and need for treatment were determined by the treating clinician and confirmed during the central screening according to iwCLL criteria.

Pre-assignment period milestones

Number of subjects started	48[1]
Number of subjects completed	41

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	not meeting Inclusion criteria or having an exclus: 5
Reason: Number of subjects	unknown: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: To verify the eligibility of patients, a central medical review of the screening data was performed and were reviewed by one of the GCLLSG study physicians together with the results of the baseline assessments in the central laboratories, including immunophenotyping and cytogenetics, for confirmation of the eligibility of the patient. 48 pats were screened and 41 enrolled.

Period 1

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

Blinding implementation details:

not applicable

Arms

Arm title	Obinutuzumab, Venetoclax and Ibrutinib

Arm description:

Patients received induction therapy with obinutuzumab (GA-101), ibrutinib, and venetoclax (GIVe) for cycles 1 through 6 and consolidation therapy with venetoclax and ibrutinib for cycles 7 through 12. Ibrutinib monotherapy was continued for cycles 13 through 36 in patients not reaching a complete response (CR) with serial undetectable minimal residual disease (uMRD) after consolidation.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	PCI 32765
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib will be administered in the mornings (before breakfast) at a daily oral dose of 420 mg as continuous therapy starting on day 1 of the first cycle, before the application of obinutuzumab is started. If MRD negativity is found in the analyses performed after cycle 9 and 12 and a complete response / complete response with incomplete recovery of the bone marrow according to iwCLL criteria could be

confirmed, treatment with ibrutinib will be terminated at cycle 15 (study visit final restaging). Ibrutinib will be continued until cycle 36 if not both of the two consecutive tests (after cycle 9 and 12) show MRD negativity or CR/CRi cannot be confirmed. The result of MRD assessment at cycle 15 is not a determinant for therapeutic decisions

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	RO5072759
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Obinutuzumab (GA101) will be applied intravenously for the first six cycles (28 days) only. During the first cycle obinutuzumab is administered on days 1 (and 2), 8 and 15. During the following cycles, it is administered on day 1.
Obinutuzumab i.v.:
Cycles 1: Day 1: Obinutuzumab 100 mg
Day 1 (or 2): Obinutuzumab 900 mg
Day 8: Obinutuzumab 1000 mg
Day 15: Obinutuzumab 1000 mg
Cycles 2-6: Day 1: Obinutuzumab 1000 mg

The first infusion of obinutuzumab (GA101) may be administered at the full dose (1000 mg) on day 1 of the first cycle if the infusion of a test-dose of 100 mg is well tolerated by the patient. Alternatively, if the first 100 mg infusion on day 1 is not tolerated well, the remaining 900 mg of the first dose should be administered on day 2.
Due to the risk of adverse events, especially infusion related reactions (IRRs) and tumor lysis syndromes (TLS), the safety measures described under section 8.2.1. of the protocol must be followed.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	1257044-40-8
Other name	ABT-199, GDC-0199
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax will be applied orally for the first twelve cycles.
Cycle 1: Days 22-28: Venetoclax 20 mg (2 tabl. at 10 mg)
Cycle 2: Days 1-7: Venetoclax 50 mg (1 tabl. at 50 mg)
Days 8-14: Venetoclax 100 mg (1 tabl. at 100 mg)
Days: 15-21: Venetoclax 200 mg (2 tabl. at 100 mg)
Days: 22-28: Venetoclax 400 mg (4 tabl. at 100 mg)
Cycles 3-12: Days 1-28: Venetoclax 400 mg (4 tabl. at 100 mg)

Due to the risk of adverse events, especially tumor lysis syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400mg is reached (ramp up). In order to prevent a TLS or diagnose it early, the safety measures described under section 8.4.3. of the protocol must be followed. On days with administration of all three study drugs, oral intake of ibrutinib (before breakfast) will be followed by oral intake of venetoclax (during breakfast), at last intravenous administration of obinutuzumab will take place.

Number of subjects in period 1	Obinutuzumab, Venetoclax and Ibrutinib
Started	41
Completed	29
Not completed	12
Adverse event, serious fatal	1

other, incl. 2 cases with MRDneg end of C12	5
Consent withdrawn by subject	1
Adverse event, non-fatal	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	26	
From 65-84 years	14	14	
85 years and over	1	1	
Age continuous Units: years			
median	62		
inter-quartile range (Q1-Q3)	54.5 to 72.5	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	24	24	
Binet Stage			
Status of the disease			
Units: Subjects			
Binet Stage A	9	9	
Binet Stage B	17	17	
Binet Stage C	15	15	
Deletion 17p			
genomic characteristic			
Units: Subjects			
no	15	15	
yes	26	26	
TP53 mutational status			
genomic characteristic			
Units: Subjects			
unmutated	2	2	
mutated	39	39	
IGHV mutational status			
genomic characeristic			
Units: Subjects			
unmutated	32	32	

mutated	6	6	
non-Evaluable	3	3	
CLL-IPI Risk Group			
risk categorization score			
Units: Subjects			
Low	0	0	
Intermediate	0	0	
High	4	4	
Very High	35	35	
missing information	2	2	
Complex Karyotype			
genomic characteristic			
Units: Subjects			
NCKT	15	15	
CKT	4	4	
HCKT	20	20	
Missing information	2	2	

End points

End points reporting groups

Reporting group title	Obinutuzumab, Venetoclax and Ibrutinib

Reporting group description:

Patients received induction therapy with obinutuzumab (GA-101), ibrutinib, and venetoclax (GIVe) for cycles 1 through 6 and consolidation therapy with venetoclax and ibrutinib for cycles 7 through 12. Ibrutinib monotherapy was continued for cycles 13 through 36 in patients not reaching a complete response (CR) with serial undetectable minimal residual disease (uMRD) after consolidation.

Primary: Complete response rate at final restaging

End point title	Complete response rate at final restaging[1]

End point description:

The primary endpoint is the complete response (CR) rate at cycle 15 (d1; final restaging) from start of therapy. The CR rate is defined by the proportion of patients having achieved a complete response (CR) or a complete response with incomplete recovery of the bone marrow (CRi) as best response (according to the IWCLL guidelines (2008)) until and including the response assessment at cycle 15 (d1; final restaging).
The primary objective of the study is to compare the null hypothesis H0: "CR rate at cycle 15 with GIVe regimen = 25%", whereby P0=25% denotes the benchmark for ineffectiveness, with the alternative H1: "CR rate at cycle 15 with GIVe regimen ≠ 25%".

End point type	Primary

End point timeframe:

The primary endpoint was analyzed after all enrolled patients who did not discontinue prematurely have achieved the cycle 15 landmark.

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: The CR rate of the GIVe regimen was compared with the benchmark of P0=25% using a two-sided one-sample binomial test.
Sixteen responders were needed to reject the null hypothesis. With 24 responders the efficacy of the GIVe-regimen can be concluded (Exact 95% Clopper-Pearson confidence-interval: 42.1%-73.7%; p-value < 0.001).

End point values	Obinutuzumab, Venetoclax and Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage				
arithmetic mean (confidence interval 95%)	58.5 (42.1 to 73.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: MRD in peripheral blood at cycle 15

End point title	MRD in peripheral blood at cycle 15

End point description:

The MRD negativity rate is defined by the proportion of patients having achieved a negative MRD level

(<10E-4) based on the full analysis set. The rate of patients with a negative, intermediate (≥10E-4 and <10E-2) and positive (≥10E-2) MRD level will be defined as the proportion of patients with negative, intermediate, and positive MRD level based on the full analysis set. Missing and not evaluable samples will be reported separately.

End point type	Secondary

End point timeframe:

Samples for evaluation of minimal residual disease (MRD) by flow cytometry from the peripheral blood (PB) were collected after cycle 15.

End point values	Obinutuzumab, Venetoclax and Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: patients				
Negative (<10E-4)	32			
Intermediate (>=10E-4 and <10E-2)	4			
Positive (>=10E-2)	0			
Missing information	4			
not evaluable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival (PFS) will be calculated until first documented disease progression (determined using standard iwCLL guidelines [2008]) or death, whichever occurs first. Patients are followed for progression-free survival at each study visit. Analyses of time-to-event endpoints will be performed using Kaplan-Meier methods. Kaplan-Meier estimates of median time and rates for 3, 6, 12, 15, 24 and 36 months after registration will be reported.

End point type	Secondary

End point timeframe:

Data for this endpoint will be collected from first study visit until last visit of each study subject.

End point values	Obinutuzumab, Venetoclax and Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage				
number (not applicable)				
3-month survival	100.0			
6-month survival	97.6			

12-month survival	95.1			
15-month survival	95.1			
24-month survival	95.1			
36-month survival	79.9			

Attachments (see zip file)	PFS_Figure/PFS_Figure CSR CLL2-GIVe.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival

End point title	Event-free survival

End point description:

Event-free survival (EFS) will be calculated until first documented disease progression (determined using standard iwCLL guidelines [2008]), death, or initiation of subsequent anti-leukemic treatment, whichever occurs first. Analyses of time- to-event endpoints will be performed using Kaplan-Meier methods. Kaplan-Meier estimates of median time and rates for 3, 6, 12, 15, 24 and 36 months after registration will be reported.

End point type	Secondary

End point timeframe:

Data for this endpoint will be collected from first study visit until last visit of each study subject.

End point values	Obinutuzumab, Venetoclax and Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage				
number (not applicable)				
3-month survival	100.0			
6-month survival	97.6			
12-month survival	95.1			
15-month survival	95.1			
24-month survival	92.6			
36-month survival	80.0			

Attachments (see zip file)	EFS_figure/EFS_Figure CSR CLL2-GIVe.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) will be calculated until death of any cause. Analyses of time-to-event endpoints will be performed using Kaplan-Meier methods. Kaplan-Meier estimates of median time and rates for 3, 6, 12, 15, 24 and 36 months after registration will be reported.

End point type	Secondary

End point timeframe:

Data for this endpoint will be collected from first study visit until last visit of each study subject.

End point values	Obinutuzumab, Venetoclax and Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage				
number (not applicable)				
3-month survival	100.0			
6-month survival	97.6			
12-month survival	95.1			
15-month survival	95.1			
24-month survival	95.1			
36-month survival	92.6			

Attachments (see zip file)	OS_Figure/OS_Figure CSR CLL2-GIVe.PNG

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	GIVe patients

Reporting group description: -

Serious adverse events	GIVe patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 41 (60.98%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign female reproductive tract neoplasm	Additional description: Benign female reproductive tract neoplasm		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer	Additional description: Ovarian cancer		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Richter's syndrome	Additional description: Richter's syndrome		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Colonoscopy	Additional description: Colonoscopy		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatic specific antigen increased	Additional description: Prostatic specific antigen increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Fractured sacrum	Additional description: Fractured sacrum		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture	Additional description: Upper limb fracture		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia	Additional description: Ventricular arrhythmia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Bladder lesion excision	Additional description: Bladder lesion excision		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hernia	Additional description: Hernia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fissure	Additional description: Anal fissure		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage	Additional description: Gastric haemorrhage		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal haematoma	Additional description: Renal haematoma		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cerebral aspergillosis	Additional description: Cerebral aspergillosis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis escherichia	Additional description: Cystitis escherichia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epididymitis	Additional description: Epididymitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis norovirus	Additional description: Gastroenteritis norovirus		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis	Additional description: Laryngitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parotitis	Additional description: Parotitis		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Progressive multifocal leukoencephalopathy	Additional description: Progressive multifocal leukoencephalopathy		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis	Additional description: Pyelonephritis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis	Additional description: Staphylococcal sepsis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis	Additional description: Urosepsis		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection	Additional description: Viral infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GIVe patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of thyroid gland	Additional description: Benign neoplasm of thyroid gland		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vascular disorders			
Haematoma	Additional description: Haematoma		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
Hypertension	Additional description: Hypertension		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Internal haemorrhage	Additional description: Internal haemorrhage		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Chills	Additional description: Chills		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	10		
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Oedema	Additional description: Oedema		
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	7		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Pain	Additional description: Pain		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Peripheral swelling	Additional description: Peripheral swelling		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Reproductive system and breast disorders			

Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Prostatic mass	Additional description: Prostatic mass		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Scrotal swelling	Additional description: Scrotal swelling		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vulvovaginal inflammation	Additional description: Vulvovaginal inflammation		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction	Additional description: Bronchial obstruction		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Pharyngeal swelling	Additional description: Pharyngeal swelling		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pulmonary mass	Additional description: Pulmonary mass		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Psychiatric disorders			
Investigations	Additional description: Investigations		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Investigations			
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood creatine phosphokinase increased	Additional description: Blood creatine phosphokinase increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Blood phosphorus increased	Additional description: Blood phosphorus increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood uric acid increased	Additional description: Blood uric acid increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
C-reactive protein increased	Additional description: C-reactive protein increased		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Troponin increased	Additional description: Troponin increased		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Animal bite	Additional description: Animal bite		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Bone contusion	Additional description: Bone contusion		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Burn oral cavity	Additional description: Burn oral cavity		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Contusion	Additional description: Contusion		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Fall	Additional description: Fall		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	10 / 41 (24.39%)		
occurrences (all)	11		
Lumbar vertebral fracture	Additional description: Lumbar vertebral fracture		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Muscle injury	Additional description: Muscle injury		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vaccination complication	Additional description: Vaccination complication		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vascular pseudoaneurysm	Additional description: Vascular pseudoaneurysm		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	6		
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Myocardial reperfusion injury	Additional description: Myocardial reperfusion injury		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Tachyarrhythmia	Additional description: Tachyarrhythmia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Ventricular tachycardia	Additional description: Ventricular tachycardia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nervous system disorders			
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Dizziness	Additional description: Dizziness		

subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Headache	Additional description: Headache		
subjects affected / exposed	11 / 41 (26.83%)		
occurrences (all)	12		
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Migraine	Additional description: Migraine		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Presyncope	Additional description: Presyncope		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
Iron deficiency anaemia	Additional description: Iron deficiency anaemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	22 / 41 (53.66%)		
occurrences (all)	65		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	16		

Ear and labyrinth disorders			
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Otorrhoea	Additional description: Otorrhoea		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Eye disorders			
Cataract	Additional description: Cataract		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Diabetic retinopathy	Additional description: Diabetic retinopathy		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Photophobia	Additional description: Photophobia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	6		
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Anal fissure	Additional description: Anal fissure		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Constipation	Additional description: Constipation		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Diarrhoea	Additional description: Diarrhoea		

subjects affected / exposed	24 / 41 (58.54%)		
occurrences (all)	36		
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Flatulence	Additional description: Flatulence		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	6		
Haematochezia	Additional description: Haematochezia		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Nausea	Additional description: Nausea		
subjects affected / exposed	11 / 41 (26.83%)		
occurrences (all)	15		
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Swollen tongue	Additional description: Swollen tongue		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Hepatobiliary disorders			
Gallbladder polyp	Additional description: Gallbladder polyp		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hepatic cyst	Additional description: Hepatic cyst		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Hepatic steatosis	Additional description: Hepatic steatosis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Dry skin	Additional description: Dry skin		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nail bed inflammation	Additional description: Nail bed inflammation		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Needle track marks	Additional description: Needle track marks		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Onychoclasis	Additional description: Onychoclasis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Petechiae	Additional description: Petechiae		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Rash	Additional description: Rash		
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	7		
Rosacea	Additional description: Rosacea		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin fissures	Additional description: Skin fissures		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin induration	Additional description: Skin induration		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin lesion	Additional description: Skin lesion		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Haematuria	Additional description: Haematuria		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Incontinence	Additional description: Incontinence		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nocturia	Additional description: Nocturia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Renal impairment	Additional description: Renal impairment		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Thyroid mass	Additional description: Thyroid mass		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	10		
Arthritis	Additional description: Arthritis		

subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Flank pain	Additional description: Flank pain		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	10		
Muscle twitching	Additional description: Muscle twitching		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Myalgia	Additional description: Myalgia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Infections and infestations			
Bacterial diarrhoea	Additional description: Bacterial diarrhoea		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		

Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Ear infection	Additional description: Ear infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Escherichia infection	Additional description: Escherichia infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Folliculitis	Additional description: Folliculitis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Gastrointestinal infection	Additional description: Gastrointestinal infection		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Hordeolum	Additional description: Hordeolum		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Infection	Additional description: Infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Laryngitis	Additional description: Laryngitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Localised infection	Additional description: Localised infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Lyme disease	Additional description: Lyme disease		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	12 / 41 (29.27%)		
occurrences (all)	14		
Onychomycosis	Additional description: Onychomycosis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Otitis media	Additional description: Otitis media		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Tinea infection	Additional description: Tinea infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Tonsillitis	Additional description: Tonsillitis		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	6		
Urinary tract infection bacterial	Additional description: Urinary tract infection bacterial		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Viral infection	Additional description: Viral infection		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Vulvovaginal mycotic infection	Additional description: Vulvovaginal mycotic infection		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Folate deficiency	Additional description: Folate deficiency		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Gout	Additional description: Gout		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypercholesterolaemia	Additional description: Hypercholesterolaemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Hyperlipasaemia	Additional description: Hyperlipasaemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hyperphosphataemia	Additional description: Hyperphosphataemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hyperuricaemia	Additional description: Hyperuricaemia		

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypoalbuminaemia	Additional description: Hypoalbuminaemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vitamin B12 deficiency	Additional description: Vitamin B12 deficiency		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	Protocol Version: V1.2 (new versions of reference safety information: IB2: Venetoclax V5, Obinutuzumab V11, Ibrutinib (29.08.2016)
18 January 2018	Protocol Version: V1.3 (new version of reference safety information Ibs: Ibrutinib Ed8, Venetoclax V8.1, Obinutuzumab V12)
09 May 2019	Protocol Version: V1.4, new versions of reference safety information: IB Venetoclax Ed9, IB Ibrutinib Ed.11
21 July 2020	Protocol Version: V1.5 (new versions of reference safety information; Ibs: Ibrutinib V13, Venetoclax V12, Obinutuzumab V 14 Add1)
30 August 2021	Protocol Version: V1.5 new version of reference safety information: IBs Ibrutinib V14; Obinutuzumab V15

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35108374