

**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
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**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
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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:

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## 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:

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## 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:

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### Population of trial subjects

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#### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

Notes:

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#### 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  $\geq 18$  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 <sup>[1]</sup>
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

<b>Arm title</b>	Obinutuzumab, Venetoclax and Ibrutinib
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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.

<b>Number of subjects in period 1</b>	Obinutuzumab, Venetoclax and Ibrutinib
Started	41
Completed	29
Not completed	12
Adverse event, serious fatal	1
Consent withdrawn by subject	1

other, incl. 2 cases with MRDneg end of C12	5
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 characteristic			
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 <sup>[1]</sup>
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 ( $\geq 10E-4$  and  $< 10E-2$ ) and positive ( $\geq 10E-2$ ) 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
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End point timeframe:

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

<b>End point values</b>	Obinutuzumab, Venetoclax and Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: patients				
Negative (<10E-4)	32			
Intermediate ( $\geq 10E-4$ and $< 10E-2$ )	4			
Positive ( $\geq 10E-2$ )	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
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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
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End point timeframe:

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

<b>End point values</b>	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			

<b>Attachments (see zip file)</b>	PFS_Figure/PFS_Figure CSR CLL2-GIVe.PNG
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Event-free survival

End point title	Event-free survival
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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
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End point timeframe:

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

<b>End point values</b>	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			

<b>Attachments (see zip file)</b>	EFS_figure/EFS_Figure CSR CLL2-GIVe.PNG
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

End point title	Overall survival
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End point description:

Overall survival (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
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End point timeframe:

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

<b>End point values</b>	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			

<b>Attachments (see zip file)</b>	OS_Figure/OS_Figure CSR CLL2-GIVe.PNG
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### 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	GIVE patients
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Reporting group description: -

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

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

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

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

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

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

subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 5		
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Headache	Additional description: Headache		
subjects affected / exposed occurrences (all)	11 / 41 (26.83%) 12		
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Migraine	Additional description: Migraine		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Presyncope	Additional description: Presyncope		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5		
Iron deficiency anaemia	Additional description: Iron deficiency anaemia		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed occurrences (all)	22 / 41 (53.66%) 65		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 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 subjects affected / exposed occurrences (all)	Additional description: Hepatic steatosis 1 / 41 (2.44%) 1		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	Additional description: Alopecia 1 / 41 (2.44%) 1		
Dry skin subjects affected / exposed occurrences (all)	Additional description: Dry skin 3 / 41 (7.32%) 3		
Erythema subjects affected / exposed occurrences (all)	Additional description: Erythema 1 / 41 (2.44%) 1		
Nail bed inflammation subjects affected / exposed occurrences (all)	Additional description: Nail bed inflammation 1 / 41 (2.44%) 1		
Needle track marks subjects affected / exposed occurrences (all)	Additional description: Needle track marks 1 / 41 (2.44%) 1		
Onychoclasia subjects affected / exposed occurrences (all)	Additional description: Onychoclasia 2 / 41 (4.88%) 2		
Petechiae subjects affected / exposed occurrences (all)	Additional description: Petechiae 1 / 41 (2.44%) 1		
Pruritus subjects affected / exposed occurrences (all)	Additional description: Pruritus 4 / 41 (9.76%) 4		
Rash subjects affected / exposed occurrences (all)	Additional description: Rash 7 / 41 (17.07%) 7		
Rosacea subjects affected / exposed occurrences (all)	Additional description: Rosacea 1 / 41 (2.44%) 1		
Skin fissures	Additional description: Skin fissures		

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

subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2		
Back pain	Additional description: Back pain		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Flank pain	Additional description: Flank pain		
subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2		
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed occurrences (all)	9 / 41 (21.95%) 10		
Muscle twitching	Additional description: Muscle twitching		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Myalgia	Additional description: Myalgia		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Infections and infestations			
Bacterial diarrhoea	Additional description: Bacterial diarrhoea		
subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 6		
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 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 subjects affected / exposed occurrences (all)	Additional description: Lyme disease 1 / 41 (2.44%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: Nasopharyngitis 12 / 41 (29.27%) 14		
Onychomycosis subjects affected / exposed occurrences (all)	Additional description: Onychomycosis 1 / 41 (2.44%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	Additional description: Oral candidiasis 1 / 41 (2.44%) 1		
Oral herpes subjects affected / exposed occurrences (all)	Additional description: Oral herpes 3 / 41 (7.32%) 3		
Otitis media subjects affected / exposed occurrences (all)	Additional description: Otitis media 1 / 41 (2.44%) 1		
Pharyngitis subjects affected / exposed occurrences (all)	Additional description: Pharyngitis 1 / 41 (2.44%) 1		
Pneumonia subjects affected / exposed occurrences (all)	Additional description: Pneumonia 3 / 41 (7.32%) 3		
Rhinitis subjects affected / exposed occurrences (all)	Additional description: Rhinitis 3 / 41 (7.32%) 3		
Sinusitis subjects affected / exposed occurrences (all)	Additional description: Sinusitis 2 / 41 (4.88%) 3		
Tinea infection subjects affected / exposed occurrences (all)	Additional description: Tinea infection 1 / 41 (2.44%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	Additional description: Tonsillitis 1 / 41 (2.44%) 1		

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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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