Clinical trial results:
A prospective, open-label, multicenter phase-II trial to evaluate the efficacy and safety of a sequential regimen of bendamustine followed by GA101 (obinutuzumab), acalabrutinib (ACP-196) and ABT-199 (venetoclax) in patients with relapsed/refractory CLL (CLL2-BAAG protocol)

Summary

EudraCT number	2017-003133-28
Trial protocol	DE
Global end of trial date	26 September 2023

Results information

Result version number	v1 (current)
This version publication date	04 September 2024
First version publication date	04 September 2024

Trial information

Trial identification

Sponsor protocol code	CLL2-BAAG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03787264
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor's number: UNI-KÖLN-3403, BfArM: 4042949

Notes:

Sponsors

Sponsor organisation name	UNIVERSITY OF COLOGNE
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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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2023
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 a sequential regimen of two cycles of bendamustine, followed by a combination therapy of GA101 (obinutuzumab), acalabrutinib (ACP-196) and ABT-199 (venetoclax) in patients with relapsed/refractory CLL.

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. Chapter 8 of the protocol included sections how to prevent and manage known side effects, including detailed instruction about modifications and treatment discontinuation. The protocol includes sections with prohibited, permitted and medication used with caution for each study medication, especially for known interactions with CYP3A4 inhibitors or inducers. In particular, since the COVID pandemic had an impact on the saftey of patients treated within the BAAG protocol, detailed guidance about management of COVID19 infections have been included.

Background therapy:

The treatment landscape for relapsed/refractory CLL faced profound changes and new developments in the past years. Several targeted agents have become available for the treatment of CLL. As most of these agents are well tolerated and have different, potentially synergistic mechanisms of action, several trials evaluating different combinations and aiming at a high efficacy are under way.
The CLL2-BAAG trial evaluates a debulking with two cycles bendamustine (only for patients with a higher tumor load and without contraindications for bendamustine), followed by an induction and a maintenance treatment with the obinutuzumab, acalabrutinib and venetoclax in patients with relapsed/refractory CLL. Thus, this trial combines chemotherapy and three synergistic (antibody, BTK-inhibitor and Bcl-2 antagonist) principles of action in order to achieve deep and long-lasting remissions with a short duration of treatment.
The primary endpoint is the evaluation of the undetectable measurable residual disease (uMRD) rate in peripheral blood (PB) measured by 4-color flow cytometry at final restaging (RE) at the end of induction treatment (12 weeks after the start of the last induction cycle).
Secondary endpoints of the study include further efficacy parameters and safety assessments by type, frequency, seriousness and severity of adverse events (AEs) and their relationship to study treatment. Secondary efficacy endpoints include overall response rate (ORR) at final restaging (RE) at the end of induction treatment (12 weeks after the start of the last induction cycle), ORR after debulking and at the end of maintenance treatment, progression-free survival (PFS), event-free survival (EFS), overall survival (OS), duration of response, treatment-free survival (TFS) and time to next CLL treatment (TTNT).

Evidence for comparator:

Not applicable.

Actual start date of recruitment	14 January 2019
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: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	30
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to enroll 46 eligible patients. Between 14th January 2019 and 25th June 2020, 46 patients were enrolled. Because of a violation of the study's inclusion/exclusion criteria, 1 patient was excluded from the full analysis set (i.e. excluded from both efficacy and safety analyses).

Pre-assignment

Screening details:

A total of 49 patients were screened for eligibility and 46 patients were included in the trial. Three (3) patients were not included due to diagnoses other than CLL (n=2) and due to patient's decision (n=1).

Pre-assignment period milestones

Number of subjects started	49[1]
Number of subjects completed	46

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	Consent withdrawn by subject: 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 of immunophenotyping and cytogenetics, for confirmation of the eligibility of the patient. A total of 49 patients were screened for eligibility and 46 patients were included in the trial. Three (3) patients were not eligible and assessed as screening failures.

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	Bendamustine (optional), acalabrutinib,obinutuzumab,venetoclax

Arm description:

Two cycles of optional debulking with bendamustine were administered before induction. Obinutuzumab was started in the first induction cycle (days 1, 8, and 15), in induction cycle 2 acalabrutinib was added, and in induction cycle 3 venetoclax ramp up (over 5 weeks up to 400 mg) was initiated. All drugs were administered according to the established schedules with daily acalabrutinib, venetoclax, and obinutuzumab once every 4 weeks during induction and every 12 weeks during maintenance. Induction treatment was administered for a total of 8 cycles (i.e., 6 cycles of the triple combination) until final restaging before the patients entered the maintenance phase. Induction cycles had 28 days and maintenance cycles had 84 days. Maintenance treatment was stopped once a (clinical) complete response and undectable MRD (peripheral blood) in 2 consecutive measurements were achieved, at progression, intolerable toxicity, or
after the maximum number of 8 cycles of maintenance treatment.

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	ribomustin
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients should receive both cycles of debulking treatment even if the patient´s tumor burden is reduced. In each of the two cycles, bendamustine is administered intravenously on two consecutive days, the cycle is repeated after 28 days.

Debulking cycles 1-2:
Day 1 bendamustine 70mg/m² i.v.,
day 2 bendamustine 70mg/m² i.v..

Investigational medicinal product name	Acalabrutinib
Investigational medicinal product code	
Other name	Calquence
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The continuous daily administration with acalabrutinib (ACP-196) starts on day 1 of induction cycle 2 under supervision of a study physician and before treatment with obinutuzumab.

Induction cycles 2-6, days 1-28: Acalabrutinib 100mg p.o. twice daily.

Before the start of the maintenance treatment, two staging assessments (initial response assessment [4 weeks after the start of the last induction cycle] and final restaging [12 weeks after the start of the last induction cycle]) will be performed. During this phase of staging, the intake of acalabrutinib is continued and there is no interruption between induction and maintenance treatment.
In the maintenance treatment acalabrutinib will be continued at the same dosage.

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	GA 101
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction cycle 1: Day 1 obinutuzumab 100mg i.v.,
day 1 (or 2) obinutuzumab 900mg i.v.,
day 8 obinutuzumab 1000mg i.v.,
day 15 obinutuzumab 1000mg i.v..
Induction cycles 2-6: Day 1 obinutuzumab 1000mg i.v..
Maintenance cycles 1-8: Day 1 obinutuzumab 1000mg i.v..

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	ABT 199
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The daily intake of venetoclax starts with a weekly dose ramp-up to final dose on day 1 of induction cycle 3. Patients will receive the first dosage of venetoclax on day 1 of induction cycle 3 in clinic/outpatient clinic/private practice before the start of the administration of obinutuzumab.
Induction cycle 3: Days 1-7 venetoclax 20mg (2 tabl. at 10mg),
days 8-14 venetoclax 50mg (1 tabl. at 50mg),
days 15-21 venetoclax 100mg (1 tabl. at 100mg),
days: 22-28 venetoclax 200mg (2 tabl. at 100mg).
Induction cycles 4-6: Days 1-28 venetoclax 400mg (4 tabl. at 100mg).
Before the start of the maintenance treatment, two staging assessments (initial response assessment [4 weeks after the start of the last induction cycle] and final restaging [12 weeks after the start of the last induction cycle]) will be performed. During this phase of staging, the intake of venetoclax is continued at the same dosage. There is no interruption between induction and maintenance treatment.

Number of subjects in period 1	Bendamustine (optional), acalabrutinib,obinutuzumab,venetoclax
Started	46
Completed	34
Not completed	12
Physician decision	1
Adverse event, non-fatal	8
Progressive disease	1
New CLL treatment (stem cell transplantation))	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	46	46	
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)	30	30	
From 65-84 years	16	16	
85 years and over	0	0	
Age continuous Units: years			
median	60.5		
inter-quartile range (Q1-Q3)	53 to 67	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	33	33	
Presence of deletion in 17p			
Cytogenetic risk factor			
Units: Subjects			
No	36	36	
Yes	9	9	
Missing information	1	1	
IGHV mutational status			
Cytogenetic risk factor			
Units: Subjects			
Unmutated	35	35	
Mutated	11	11	
CLL-IPI risk group			
International prognostic index used for CLL			
Units: Subjects			
Low	3	3	
Intermediate	16	16	
High	13	13	
Very high	12	12	
Missing information	2	2	
TP53 mutational status			

Cytogenetic risk factor			
Units: Subjects			
Unmutated	32	32	
Mutated	13	13	
Missing information	1	1	
Binet stage			
Status of the disease			
Units: Subjects			
Binet A	16	16	
Binet B	16	16	
Binet C	14	14	
Cumulative illness rating scale (CIRS)			
Validated score to evaluate the comorbidity			
Units: Scores			
median	3		
inter-quartile range (Q1-Q3)	1 to 5	-	
Observation time			
Time between trial registration and last observation or death			
Units: Months			
median	36.3		
inter-quartile range (Q1-Q3)	35.2 to 38.0	-	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The full analysis set (FAS) includes all patients enrolled into the trial who received at least 3 cycles of induction therapy. This means that at least one dose of any compound of the trial medication has to be documented for the third cycle of induction treatment.
In total, 46 patients have been enrolled at the end of recruitment. One patient was excluded from the study due to subsequently detected violation of inclusion/exclusion-criteria. This patient was also excluded from the full analysis set, i.e. this patient was excluded from efficacy and safety analyses.

Reporting group values	Full analysis set		
Number of subjects	45		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	30		
From 65-84 years	15		
85 years and over	0		
Age continuous Units: years			
median	60		
inter-quartile range (Q1-Q3)	53 to 66		

Gender categorical Units: Subjects			
Female	13		
Male	32		
Presence of deletion in 17p			
Cytogenetic risk factor			
Units: Subjects			
No	36		
Yes	8		
Missing information	1		
IGHV mutational status			
Cytogenetic risk factor			
Units: Subjects			
Unmutated	34		
Mutated	11		
CLL-IPI risk group			
International prognostic index used for CLL			
Units: Subjects			
Low	3		
Intermediate	16		
High	13		
Very high	11		
Missing information	2		
TP53 mutational status			
Cytogenetic risk factor			
Units: Subjects			
Unmutated	32		
Mutated	13		
Missing information	0		
Binet stage			
Status of the disease			
Units: Subjects			
Binet A	16		
Binet B	16		
Binet C	13		
Cumulative illness rating scale (CIRS)			
Validated score to evaluate the comorbidity			
Units: Scores median inter-quartile range (Q1-Q3)	 2 1 to 4.5		
Observation time			
Time between trial registration and last observation or death			
Units: Months median inter-quartile range (Q1-Q3)	 36.3 35.3 to 38.0		

End points

End points reporting groups

Reporting group title	Bendamustine (optional), acalabrutinib,obinutuzumab,venetoclax

Reporting group description:

Two cycles of optional debulking with bendamustine were administered before induction. Obinutuzumab was started in the first induction cycle (days 1, 8, and 15), in induction cycle 2 acalabrutinib was added, and in induction cycle 3 venetoclax ramp up (over 5 weeks up to 400 mg) was initiated. All drugs were administered according to the established schedules with daily acalabrutinib, venetoclax, and obinutuzumab once every 4 weeks during induction and every 12 weeks during maintenance. Induction treatment was administered for a total of 8 cycles (i.e., 6 cycles of the triple combination) until final restaging before the patients entered the maintenance phase. Induction cycles had 28 days and maintenance cycles had 84 days. Maintenance treatment was stopped once a (clinical) complete response and undectable MRD (peripheral blood) in 2 consecutive measurements were achieved, at progression, intolerable toxicity, or
after the maximum number of 8 cycles of maintenance treatment.

Subject analysis set title	Full analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The full analysis set (FAS) includes all patients enrolled into the trial who received at least 3 cycles of induction therapy. This means that at least one dose of any compound of the trial medication has to be documented for the third cycle of induction treatment.
In total, 46 patients have been enrolled at the end of recruitment. One patient was excluded from the study due to subsequently detected violation of inclusion/exclusion-criteria. This patient was also excluded from the full analysis set, i.e. this patient was excluded from efficacy and safety analyses.

Primary: Undetectable measurable residual disease (uMRD) rate in peripheral blood at final restaging after end of induction treatment

End point title	Undetectable measurable residual disease (uMRD) rate in peripheral blood at final restaging after end of induction treatment[1]

End point description:

Undetectable measurable residual disease (uMRD) is defined as less than 1 CLL cell among 10.000 leukocytes, i.e. <10-4. The uMRD rate is defined as the proportion of patients having achieved uMRD by 4-color flow cytometry at final restaging based on the full analysis set. The corresponding 95% confidence interval will be calculated according to Clopper-Pearson.
The primary objective of the study is to test the null hypothesis H0: "uMRD rate <=70%" (with corresponding alternative hypothesis H1: "uMRD rate >70%") by comparing the uMRD rate with the benchmark of P0=70% using a one-sided one-sample binomial test and a pre-specified significance level of 2.5%. The efficacy of the study treatment will be concluded if the null hypothesis is rejected.

End point type	Primary

End point timeframe:

At final restaging, which is 12 weeks after the last cycle of induction treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The uMRD rate in peripheral blood at final restaging after end of induction treatment was compared with the benchmark of P0=70% using a one-sided one-sample binomial test: P = 0.258.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Percentage				
number (not applicable)				
uMRD rate	75.6			
95% confidence interval: lower bound	60.5			

95% confidence interval: upper bound	87.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS) will be calculated from the date of registration until first documented disease progression (as defined by the IWCLL response criteria [2008] and unless documented before start of the induction treatment) or death by any cause, whichever occurs first. These will be counted as events for PFS. The initiation of a subsequent CLL treatment after the study treatment will not be counted as an event or as a reason for censoring. Patients who have not experienced disease progression or death will be censored at the date of the last response/tumor assessment they were assessed as being event-free. If no response/tumor assessments were documented after registration, patients will be censored at the time of registration + 1 day.
Analysis of PFS will be performed descriptively (i.e. without confirmatory testings) using Kaplan-Meier methodology. Kaplan-Meier estimates of rates for 12, 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	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Percentage				
number (not applicable)				
12-month survival	95.6			
24-month survival	95.6			
36-month survival	85.0			

Attachments (see zip file)	Progression-free survival (PFS)/CLL2-BAAG_PFS_20240123.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next treatment (TTNT)

End point title	Time to next treatment (TTNT)

End point description:

Time to next treatment (TTNT) will be calculated from the date of registration until initiation of subsequent anti-leukemic treatment. These will be counted as events for TTNT. Alive patients for whom

no subsequent anti-leukemic tratment is documented will be censored at the date of last observation they were assessed as being event-free. Deceased patients for whom no subsequent anti-leukemic treatment is documented will be censored at the date of death. If no visits were documented after registration, patients will be censored at the time of registration + 1 day.
Analysis of TTNT will be performed descriptively (i.e. without confirmatory testings) using Kaplan-Meier methodology. Kaplan-Meier estimates of rates for 12, 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	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Percentage				
number (not applicable)				
12-month survival	97.8			
24-month survival	95.5			
36-month survival	85.9			

Attachments (see zip file)	Time to next treatment (TTNT)/CLL2-BAAG_TTNT_20240123.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) will be calculated from the date of registration until death by any cause. These will be counted as events for OS. Alive patients will be censored at the date of last observation. If no visits were documented after registration, patients will be censored at the time of registration + 1 day.
Analysis of OS will be performed descriptively (i.e. without confirmatory testings) using Kaplan-Meier methodology. Kaplan-Meier estimates for 12, 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	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Percentage				
number (not applicable)				
12-month survival	100.0			

24-month survival	100.0			
36-month survival	93.8			

Attachments (see zip file)	Overall survival (OS)/CLL2-BAAG_OS_20240123.png

Statistical analyses

No statistical analyses for this end point

Secondary: Response at final restaging after end of induction treatment

End point title	Response at final restaging after end of induction treatment

End point description:

Response at final restaging after end of induction treatment will be analyzed descriptively (i.e. without confirmatory testings).

End point type	Secondary

End point timeframe:

At final restaging, which 12 weeks after the last cycle of induction treatment.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Patients				
Complete response (CR)	6			
Partial response (PR)	39			
Stable disease (SD)	0			
Progressive disease (PD)	0			

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	RR patient

Reporting group description: -

Serious adverse events	RR patient		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 45 (62.22%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease	Additional description: Hodgkin's disease		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large granular lymphocytosis	Additional description: Large granular lymphocytosis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma metastatic	Additional description: Pancreatic carcinoma metastatic		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer	Additional description: Prostate cancer		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Richter's syndrome	Additional description: Richter's syndrome		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Granulomatosis with polyangiitis	Additional description: Granulomatosis with polyangiitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Incisional hernia	Additional description: Incisional hernia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele	Additional description: Hydrocele		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebral cyst	Additional description: Cerebral cyst		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial nerve disorder	Additional description: Facial nerve disorder		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia	Additional description: Autoimmune haemolytic anaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Sudden hearing loss	Additional description: Sudden hearing loss		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis	Additional description: Gastritis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mechanical ileus	Additional description: Mechanical ileus		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis	Additional description: Cholelithiasis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urethral stenosis	Additional description: Urethral stenosis		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Atypical pneumonia	Additional description: Atypical pneumonia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19	Additional description: COVID-19		
subjects affected / exposed	6 / 45 (13.33%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
COVID-19 pneumonia	Additional description: COVID-19 pneumonia		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
Groin abscess	Additional description: Groin abscess		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonsillar abscess	Additional description: Peritonsillar abscess		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Septic shock	Additional description: Septic shock		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	RR patient		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma	Additional description: Haemangioma		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Haemangioma of liver	Additional description: Haemangioma of liver		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vascular disorders			
Arteriosclerosis	Additional description: Arteriosclerosis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Haematoma	Additional description: Haematoma		
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Hypertension	Additional description: Hypertension		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Spider vein	Additional description: Spider vein		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills	Additional description: Chills		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Drug intolerance	Additional description: Drug intolerance		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Fatigue	Additional description: Fatigue		

subjects affected / exposed	17 / 45 (37.78%)		
occurrences (all)	18		
Extravasation	Additional description: Extravasation		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oedema	Additional description: Oedema		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pain	Additional description: Pain		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Allergy to arthropod bite	Additional description: Allergy to arthropod bite		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypogammaglobulinaemia	Additional description: Hypogammaglobulinaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Immunodeficiency	Additional description: Immunodeficiency		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Postmenopausal haemorrhage	Additional description: Postmenopausal haemorrhage		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Asthma		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bronchitis chronic	Additional description: Bronchitis chronic		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cough	Additional description: Cough		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	5		
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Productive cough	Additional description: Productive cough		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Psychiatric disorders			

Depression	Additional description: Depression		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Product issues			
Device deposit issue	Additional description: Device deposit issue		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Enterobacter test positive	Additional description: Enterobacter test positive		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Escherichia test positive	Additional description: Escherichia test positive		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite	Additional description: Animal bite		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	19 / 45 (42.22%)		
occurrences (all)	19		
Ligament sprain	Additional description: Ligament sprain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin abrasion	Additional description: Skin abrasion		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Thoracic vertebral fracture	Additional description: Thoracic vertebral fracture		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Transfusion reaction	Additional description: Transfusion reaction		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Wound	Additional description: Wound		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Von Willebrand's disease	Additional description: Von Willebrand's disease		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations	Additional description: Palpitations		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		

Ventricular extrasystoles	Additional description: Ventricular extrasystoles		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness	Additional description: Dizziness		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Headache	Additional description: Headache		
subjects affected / exposed	12 / 45 (26.67%)		
occurrences (all)	17		
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Olfactory nerve disorder	Additional description: Olfactory nerve disorder		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Sciatica	Additional description: Sciatica		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Taste disorder	Additional description: Taste disorder		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anaemia	Additional description: Anaemia		
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Aplasia pure red cell	Additional description: Aplasia pure red cell		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	18		
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	19 / 45 (42.22%)		
occurrences (all)	28		
Ear and labyrinth disorders			
Hypoacusis	Additional description: Hypoacusis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vertigo positional	Additional description: Vertigo positional		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Eye disorders			
Blepharospasm	Additional description: Blepharospasm		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Ocular hyperaemia	Additional description: Ocular hyperaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Visual impairment	Additional description: Visual impairment		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Abdominal pain lower	Additional description: Abdominal pain lower		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Barrett's oesophagus	Additional description: Barrett's oesophagus		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Constipation	Additional description: Constipation		
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	7		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	17 / 45 (37.78%)		
occurrences (all)	27		
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Flatulence	Additional description: Flatulence		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Gingival bleeding	Additional description: Gingival bleeding		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		

Glossitis	Additional description: Glossitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastritis	Additional description: Gastritis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Mouth haemorrhage	Additional description: Mouth haemorrhage		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nausea	Additional description: Nausea		
subjects affected / exposed	12 / 45 (26.67%)		
occurrences (all)	18		
Periodontal disease	Additional description: Periodontal disease		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hepatobiliary disorders			
hepatoloxicity	Additional description: hepatoloxicity		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Dermatitis atopic	Additional description: Dermatitis atopic		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Drug eruption	Additional description: Drug eruption		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Dry skin	Additional description: Dry skin		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Lichen planus	Additional description: Lichen planus		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Night sweats	Additional description: Night sweats		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Petechiae	Additional description: Petechiae		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Rash	Additional description: Rash		
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	12		
Skin lesion	Additional description: Skin lesion		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin mass	Additional description: Skin mass		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vitiligo	Additional description: Vitiligo		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nephrolithiasis	Additional description: Nephrolithiasis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Renal impairment	Additional description: Renal impairment		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Arthritis	Additional description: Arthritis		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Back pain	Additional description: Back pain		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Bone pain	Additional description: Bone pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Flank pain	Additional description: Flank pain		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Kyphosis	Additional description: Kyphosis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Myalgia	Additional description: Myalgia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Neck pain	Additional description: Neck pain		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Osteoporosis	Additional description: Osteoporosis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Infections and infestations			
Abscess	Additional description: Abscess		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Acarodermatitis	Additional description: Acarodermatitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bacterial vaginosis	Additional description: Bacterial vaginosis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Catheter site infection	Additional description: Catheter site infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	8		
COVID-19	Additional description: COVID-19		
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	10		
COVID-19 pneumonia	Additional description: COVID-19 pneumonia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Furuncle	Additional description: Furuncle		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		

Gastrointestinal infection	Additional description: Gastrointestinal infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Genital herpes	Additional description: Genital herpes		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Implant site infection	Additional description: Implant site infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Infection	Additional description: Infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nail bed infection	Additional description: Nail bed infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	10		
Otitis media	Additional description: Otitis media		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Pneumonia parainfluenzae viral	Additional description: Pneumonia parainfluenzae viral		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pneumonia pneumococcal	Additional description: Pneumonia pneumococcal		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pyelonephritis	Additional description: Pyelonephritis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Rhinovirus infection	Additional description: Rhinovirus infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	12		
Vaginal infection	Additional description: Vaginal infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Abnormal loss of weight	Additional description: Abnormal loss of weight		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Diabetes mellitus	Additional description: Diabetes mellitus		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyperlipasaemia	Additional description: Hyperlipasaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypercreatininaemia	Additional description: Hypercreatininaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyperamylasaemia	Additional description: Hyperamylasaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypophosphataemia	Additional description: Hypophosphataemia		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Iron deficiency	Additional description: Iron deficiency		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2018	The protocol was amended and Protocol Version: v1.2 was approved: Duration of SAE Reporting was amended.
06 January 2020	Due to the new safety documents for acalabrutinib, bendamustine, obinutuzumab and venetoclax, some changes to the study protocol and patient information were necessary; in addition, an addendum was created for patients already included in the study. Furthermore, some necessary adjustments were made to the study protocol with regard to the planned safety analysis and the change of a financial sponsor. In October 2019, the safety analysis of the first 6 patients who were treated for at least 8 weeks with the triple combination of obinutuzumab, acalabrutinib and venetoclax was carried out as planned in the protocol. It showed no unexpected or cumulative toxicities, but a very favourable safety profile. The members of the CLL2-BAAG protocol committee assessed the AEs/ SAEs that occurred and indicated that there were no safety concerns with the triple combination and that enrolment could continue without restrictions or new safety precautions. Thus, further recruitment was carried out without limitation. There was also a change of financial sponsor from Acerta to AstraZeneca, as AstraZeneca acquired a majority stake in Acerta and the Acalabruntinb programme for externally sponsored studies was transferred to AstraZeneca. This does not result in any changes to the investigational product acalabrutinib or its manufacture.
16 March 2021	Due to the new safety documents for acalabrutinib, obinutuzumab and venetoclax changes to the patient information were necessary; these relate to acalabrutinib and obinutuzumab. As recruitment for the trial has already been completed and no new patients will be included in the trial, only an addendum was created for all patients included in the trial. In future, the Summary of Product Characteristics will be used as the reference document for acalabrutinib instead of the IB.
02 June 2022	Due to new safety documents for bendamustine, acalabrutinib, obinutuzumab and venetoclax, changes to the patient information were necessary; these relate to acalabrutinib and obinutuzumab. As enrolment of the study has already been completed and no new patients are being included in the study, only an addendum to the patient information was created for all patients included in the study. Furthermore, a new section on the benefit-risk assessment of the Covid-19 pandemic, including vaccinations and passive immunisation, and a new section on additional scientific investigations on blood samples already taken were added to the protocol. The corresponding consent of the patients is also requested in the addendum to the patient information.
14 September 2022	In addition to the amended protocol, the new SmPCs for venetoclax (March 2022), obinutuzumab (April 2022 & July 2022) and bendamustine (February 2022).were submitted. According to the Sponsor's assessment, the changes in the new Summary of Product Characteristics for venetoclax (March 2022), obinutuzumab (July 2022) and bendamustine (February 2022) are only of a formal nature and therefore not substantive. The substantial amendments regarding the side effects of the Obinutuzumab SmPC were already incorporated into the protocol in the previous amendment. A table showing the changes to the individual SmPCs and the sponsor assessment is attached.
04 April 2023	(Non-Substantial Amendment) Submission of new RSI for Obinutuzumab SmPC 12/2022 ; Acalabrutinib SmPC 01/2023; Venetoclax SmPC 02/2023; Bendamustin SmPC 07/2022

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38620072

http://www.ncbi.nlm.nih.gov/pubmed/35988545