Clinical trial results:
A Phase Ib/II combination trial of acalabrutinib with rituximab, cyclophosphamide, doxorubicin,vincristine and prednisolone (R-CHOP) for patients with diffuse large B-cell lymphoma (DLBCL)

Summary

EudraCT number	2015-003213-18
Trial protocol	GB
Global end of trial date	23 March 2023

Results information

Result version number	v1 (current)
This version publication date	24 May 2025
First version publication date	24 May 2025

Trial information

Trial identification

Sponsor protocol code	RHMCAN1129

Additional study identifiers

ISRCTN number	ISRCTN13626902
ClinicalTrials.gov id (NCT number)	NCT03571308
WHO universal trial number (UTN)	-
Other trial identifiers	CR UK Trial Number: CRUKDE/16/006

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	Clinical Trials Unit, Southampton, United Kingdom, SO16 6YD
Public contact	Ailsa Duckworth, University Hospital Southampton NHS Foundation Trust, 44 023 8120 5131 , ailsa.duckworth@uhs.nhs.uk
Scientific contact	Ailsa Duckworth, University Hospital Southampton NHS Foundation Trust, 44 023 8120 5131 , ailsa.duckworth@uhs.nhs.uk

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	30 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2023
Global end of trial reached?	Yes
Global end of trial date	23 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective at Stage 1 is to:
1. Examine the safety and toxicity profile of acalabrutinib in combination with R-CHOP and define the dose limiting toxicity (DLT) or maximum administered dose (MAD).

The primary objective at Stage 2 is to:
2. To document the anti-tumour activity of acalabrutinib in combination with R-CHOP in patients with previously untreated CD20 positive DLBCL.
3. To determine additional safety information on acalabrutinib in combination with R-CHOP.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	0

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)	19
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 25 May 2017 to 02 Jan 2020, 38 participants (14 in Phase I and 24 in Phase II) were registered at 7 sites, and 7 patients were ineligible.

Pre-assignment

Screening details:

From May 2017 to Jan 2020, 38 pts. were enrolled (safety population: pts. in receipt of any component of therapy). Seven of the enrolled pts. were found to be ineligible (insufficient material for translational work, 2pts.; taking a proton pump inhibitor during therapy, 2 pts.; follicular histology, 1pt.; abnormal LFTs at baseline, 1pt.; age >65).

Period 1

Period 1 title	Phase 1 and Phase 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

The patients will receive a first cycle of R-CHOP. Acalabrutinib, at a starting dose of 100 mg od, will be added from cycle 2 to 6. This will be followed by cycles 7 and 8 of acalabrutinib only 100mg od for 28 days for each cycle. Dose escalation to 200 mg daily (100 mg bd) of acalabrutinib will be decided by the Safety Review Committee based on safety data and patients' compliance assessment.

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

Dosage and administration details:

Acalabrutinib, at a starting dose of 100 mg od, will be added from cycle 2 to 6. This will be followed by cycles 7 and 8 of acalabrutinib only 100mg od for 28 days for each cycle.

Arm title	Cohort 2 and Phase 2 patients

Arm description:

The first 6 patients of cohort 2 will start acalabrutinib + R-CHOP at the daily dose of 200mg administered as 100mg bd from cycle 2 after the Safety Review Committee has approved dose escalation based on all the safety data from cohort 1. After all patients of cohort 2 have completed their 2nd cycle of acalabrutinib + R-CHOP (3rd cycle of therapy), and based on patients' safety data, compliance assessment, PK/PD measures if available, the Safety Review Committee will assess the safety of 200mg. If one or two instances of DLT is observed among the initial six patients of cohort 2, the cohort will be expanded to a further six patients. Depending on tolerability as set out, cohort 2 patients should receive cycle 1 of R-CHOP, cycles 2-6 R-CHOP plus acalabrutinib and then cycles 7 and 8 of acalabrutinib only at 200mg administered as 100mg bd.

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

Dosage and administration details:

The first 6 patients of cohort 2 will start acalabrutinib + R-CHOP at the daily dose of 200mg

administered as 100mg bd from cycle 2 after the Safety Review Committee has approved dose escalation based on all the safety data from cohort 1. After all patients of cohort 2 have completed their 2nd cycle of acalabrutinib + R-CHOP (3rd cycle of therapy), and based on patients' safety data, compliance assessment, PK/PD measures if available, the Safety Review Committee will assess the safety of 200mg. If one or two instances of DLT is observed among the initial six patients of cohort 2, the cohort will be expanded to a further six patients. Depending on tolerability as set out, cohort 2 patients should receive cycle 1 of R-CHOP, cycles 2-6 R-CHOP plus acalabrutinib and then cycles 7 and 8 of acalabrutinib only at 200mg administered as 100mg bd.

Number of subjects in period 1	Cohort 1	Cohort 2 and Phase 2 patients
Started	7	24
Completed	4	22
Not completed	3	2
Consent withdrawn by subject	1	1
Death	1	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1

Reporting group description:

The patients will receive a first cycle of R-CHOP. Acalabrutinib, at a starting dose of 100 mg od, will be added from cycle 2 to 6. This will be followed by cycles 7 and 8 of acalabrutinib only 100mg od for 28 days for each cycle. Dose escalation to 200 mg daily (100 mg bd) of acalabrutinib will be decided by the Safety Review Committee based on safety data and patients' compliance assessment.

Reporting group title	Cohort 2 and Phase 2 patients

Reporting group description:

The first 6 patients of cohort 2 will start acalabrutinib + R-CHOP at the daily dose of 200mg administered as 100mg bd from cycle 2 after the Safety Review Committee has approved dose escalation based on all the safety data from cohort 1. After all patients of cohort 2 have completed their 2nd cycle of acalabrutinib + R-CHOP (3rd cycle of therapy), and based on patients' safety data, compliance assessment, PK/PD measures if available, the Safety Review Committee will assess the safety of 200mg. If one or two instances of DLT is observed among the initial six patients of cohort 2, the cohort will be expanded to a further six patients. Depending on tolerability as set out, cohort 2 patients should receive cycle 1 of R-CHOP, cycles 2-6 R-CHOP plus acalabrutinib and then cycles 7 and 8 of acalabrutinib only at 200mg administered as 100mg bd.

Reporting group values	Cohort 1	Cohort 2 and Phase 2 patients	Total
Number of subjects	7	24	31
Age categorical Units: Subjects			
Adults (18-64 years)	1	18	19
Over 65	6	6	12
Age continuous Units: years			
arithmetic mean	70.9	55.7	
standard deviation	± 4.4	± 13.5	-
Gender categorical Units: Subjects			
Female	1	6	7
Male	6	18	24
ECOG performance status Units: Subjects			
Fully active	2	14	16
Restricted in physically strenuous activity	3	9	12
Capable of all self-care but unable to work	2	1	3
Capable of only limited self-care	0	0	0

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

The patients will receive a first cycle of R-CHOP. Acalabrutinib, at a starting dose of 100 mg od, will be added from cycle 2 to 6. This will be followed by cycles 7 and 8 of acalabrutinib only 100mg od for 28 days for each cycle. Dose escalation to 200 mg daily (100 mg bd) of acalabrutinib will be decided by the Safety Review Committee based on safety data and patients' compliance assessment.

Reporting group title	Cohort 2 and Phase 2 patients

Reporting group description:

The first 6 patients of cohort 2 will start acalabrutinib + R-CHOP at the daily dose of 200mg administered as 100mg bd from cycle 2 after the Safety Review Committee has approved dose escalation based on all the safety data from cohort 1. After all patients of cohort 2 have completed their 2nd cycle of acalabrutinib + R-CHOP (3rd cycle of therapy), and based on patients' safety data, compliance assessment, PK/PD measures if available, the Safety Review Committee will assess the safety of 200mg. If one or two instances of DLT is observed among the initial six patients of cohort 2, the cohort will be expanded to a further six patients. Depending on tolerability as set out, cohort 2 patients should receive cycle 1 of R-CHOP, cycles 2-6 R-CHOP plus acalabrutinib and then cycles 7 and 8 of acalabrutinib only at 200mg administered as 100mg bd.

Primary: Overall response rate (efficacy population)

End point title	Overall response rate (efficacy population)

End point description:

The overall response has been assessed, the overall response according to the investigator's overall response assessment at the end of treatment and, the primary endpoint, the overall response rate (patients with a complete or partial response). This is summarised by the groups below using the efficacy population:
- Phase 1 Cohort 1 patients only
- Phase 2 Cohort 2 patients and phase 2 patients combined

End point type	Primary

End point timeframe:

From May 2017 to June 2022 (follow up)

End point values	Cohort 1	Cohort 2 and Phase 2 patients		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[1]	24		
Units: Number of patients				
Complete response	4	19		
Partial response	1	4		
Stable disease	0	1		
Progressive disease	1	0		

Notes:

[1] - Cohort 1 - 1 Subject withdrawal (EOT visit did not take place)

Statistical analyses

Statistical analysis title	Primary endpoint - Overall response rate - Cohort1
Statistical analysis description:	
Primary endpoint - Overall response rate of the combination acalabrutinib and R-CHOP - Cohort 1 only	
Comparison groups	Cohort 1 v Cohort 2 and Phase 2 patients
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
Method	95% confidence intervals exact method
Parameter estimate	Response rate
Point estimate	83.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.9
upper limit	99.6
Variability estimate	Standard deviation

Statistical analysis title	Cohort 2 Primary endpoint - Overall response
Statistical analysis description:	
Primary endpoint - Overall response rate of the combination acalabrutinib and R-CHOP for Cohort 2 only	
Comparison groups	Cohort 2 and Phase 2 patients v Cohort 1
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Method	95% confidence intervals exact method
Parameter estimate	Response rate
Point estimate	95.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	78.9
upper limit	99.9
Variability estimate	Standard deviation

Secondary: Deaths, Progressions and Event Information (efficacy population)

End point title	Deaths, Progressions and Event Information (efficacy population)

End point description:

The post-treatment survival and progression information which includes the number of deaths, number of progressions, number of EFS events and the number of TTF events on the trial. This includes any deaths or progressions or events that were recorded at any time from date of treatment initiation to the end of study.
The tables and secondary endpoint analysis have been carried out using the efficacy population split by the following two groups:
• Cohort 1 patients only
• Cohort 2 patients and phase 2 patients combined

End point type	Secondary

End point timeframe:
From May 2017 to June 2022 (follow up)

End point values	Cohort 1	Cohort 2 and Phase 2 patients		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	24		
Units: Number of patients				
Number of deaths	1	1		
Number of progressions	1	1		
Number of PFS events	1	1		
Number of EFS events	2	2		
Number of TTF events (any treatment failure includ	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS at 6, 9, 12 and 24 months (efficacy population)

End point title	PFS at 6, 9, 12 and 24 months (efficacy population)

End point description:

End point type	Secondary

End point timeframe:
From May 2017 to June 2022

End point values	Cohort 1	Cohort 2 and Phase 2 patients		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	24		
Units: percent				
number (confidence interval 95%)				
PFS at 6 months	80 (20.40 to 96.9)	100 (100 to 100)		
PFS at 9 months	80 (20.4 to 96.9)	100 (100 to 100)		
PFS at 12 months	80 (20.4 to 96.9)	94.7 (68.1 to 99.2)		
PFS at 24 months	80 (20.4 to 96.9)	94.7 (68.1 to 99.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS at 6, 9, 12 and 24 months (efficacy population)

End point title	OS at 6, 9, 12 and 24 months (efficacy population)

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2 and Phase 2 patients		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	24		
Units: percent				
number (confidence interval 95%)				
OS at 6 months	100 (100 to 100)	100 (100 to 100)		
OS at 9 months	100 (100 to 100)	100 (100 to 100)		
OS at 12 months	80.0 (20.4 to 96.9)	100 (100 to 100)		
OS at 24 months	80.0 (20.4 to 96.9)	95.7 (72.9 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: EFS at 6, 9, 12 and 24 months (efficacy population)

End point title	EFS at 6, 9, 12 and 24 months (efficacy population)

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2 and Phase 2 patients		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	24		
Units: percent				
number (confidence interval 95%)				
EFS at 6 months	80.0 (20.4 to 96.9)	100 (100 to 100)		
EFS at 9 months	60.0 (12.6 to 88.2)	95.2 (70.7 to 99.3)		
EFS at 12 months	60.0 (12.6 to 88.2)	90.2 (66.2 to 97.5)		
EFS at 24 months	60.0 (12.6 to 88.2)	90.2 (66.2 to 97.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTF at 6, 9, 12 and 24 months

End point title	TTF at 6, 9, 12 and 24 months

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Cohort 1	Cohort 2 and Phase 2 patients		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	24		
Units: percent				
number (confidence interval 95%)				
TTF at 6 months	57.1 (17.2 to 83.7)	83.3 (61.5 to 93.4)		
TTF at 9 months	42.9 (9.8 to 73.4)	79.2 (57 to 90.8)		
TTF at 12 months	42.9 (9.8 to 73.4)	74.8 (52.2 to 87.8)		
TTF at 24 months	42.9 (9.8 to 73.4)	74.8 (52.2 to 87.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting requirement for SAEs affecting participants applies for all events occurring up to 30 days after the last administration of trial drugs. All adverse events should be recorded in the relevant eCRF and submitted to SCTU.

Adverse event reporting additional description:

All unresolved adverse events should be followed by the investigator until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, each participant to report any subsequent event(s) that the participant believes might reasonably be related to participation in this trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Cohort 2
Reporting group description: -	
Reporting group title	Cohort 1

Reporting group description: -

Serious adverse events	Cohort 2	Cohort 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 24 (50.00%)	6 / 7 (85.71%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dystonia	Additional description: Dystonia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy	Additional description: Peripheral motor neuropathy		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Febrile neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: Small intestinal obstruction		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection	Additional description: Viral infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection	Additional description: Rhinovirus infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection	Additional description: Respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia	Additional description: Hypokalaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 2	Cohort 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)	7 / 7 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: Basal cell carcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension	Additional description: Hypertension		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypotension	Additional description: Hypotension		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	3 / 7 (42.86%)	
occurrences (all)	1	3	

Lymphoedema	Additional description: Lymphoedema		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Haematoma	Additional description: Haematoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Adverse drug reaction	Additional description: Adverse drug reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hernia	Additional description: Hernia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pain	Additional description: Pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 24 (45.83%)	4 / 7 (57.14%)	
occurrences (all)	18	9	
Chest pain	Additional description: Chest pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Chest discomfort	Additional description: Chest discomfort		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oedema	Additional description: Oedema		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pyrexia	Additional description: Pyrexia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Axillary pain	Additional description: Axillary pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral	Additional description: Oedema peripheral		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Nipple pain	Additional description: Nipple pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Breast swelling	Additional description: Breast swelling		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gynaecomastia	Additional description: Gynaecomastia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Sinus congestion	Additional description: Sinus congestion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Dyspnoea	Additional description: Dyspnoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	5	2	
Upper respiratory tract congestion	Additional description: Upper respiratory tract congestion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea	Additional description: Rhinorrhoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Cough	Additional description: Cough		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Epistaxis	Additional description: Epistaxis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 24 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Insomnia	Additional description: Insomnia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	1 / 7 (14.29%)	
occurrences (all)	2	2	
Claustrophobia	Additional description: Claustrophobia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Depression	Additional description: Depression		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Mood swings	Additional description: Mood swings		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Investigations			
Weight decreased	Additional description: Weight decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
White blood cell count decreased	Additional description: White blood cell count decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood sodium decreased	Additional description: Blood sodium decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Blood potassium decreased	Additional description: Blood potassium decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Hip fracture	Additional description: Hip fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Fall	Additional description: Fall		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Eye contusion	Additional description: Eye contusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Arthropod bite	Additional description: Arthropod bite		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			

subjects affected / exposed	7 / 24 (29.17%)	0 / 7 (0.00%)	
occurrences (all)	7	0	
Contusion	Additional description: Contusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Tooth fracture	Additional description: Tooth fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Femoral neck fracture	Additional description: Femoral neck fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nail injury	Additional description: Nail injury		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Myocardial infarction	Additional description: Myocardial infarction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Tachycardia	Additional description: Tachycardia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 24 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Headache	Additional description: Headache		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 24 (37.50%)	2 / 7 (28.57%)	
occurrences (all)	13	5	
Taste disorder	Additional description: Taste disorder		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Paraesthesia	Additional description: Paraesthesia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	3	2	
Dizziness postural	Additional description: Dizziness postural		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Syncope	Additional description: Syncope		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia	Additional description: Hypoaesthesia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Dizziness	Additional description: Dizziness		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	5	4	

Presyncope	Additional description: Presyncope		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Peroneal nerve palsy	Additional description: Peroneal nerve palsy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Spontaneous haematoma	Additional description: Spontaneous haematoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Neutropenia	Additional description: Neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 24 (45.83%)	5 / 7 (71.43%)	
occurrences (all)	13	5	
Increased tendency to bruise	Additional description: Increased tendency to bruise		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Anaemia	Additional description: Anaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 24 (29.17%)	1 / 7 (14.29%)	
occurrences (all)	9	2	
Thrombocytopenia	Additional description: Thrombocytopenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	7	1	
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Eye pain	Additional description: Eye pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Visual impairment	Additional description: Visual impairment		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vision blurred	Additional description: Vision blurred		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Aphthous ulcer	Additional description: Aphthous ulcer		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oral pain	Additional description: Oral pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Toothache	Additional description: Toothache		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	5	2	
Intestinal obstruction	Additional description: Intestinal obstruction		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 24 (29.17%)	2 / 7 (28.57%)	
occurrences (all)	12	2	
Abdominal pain upper	Additional description: Abdominal pain upper		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Dry mouth	Additional description: Dry mouth		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Anal haemorrhage	Additional description: Anal haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Large intestine perforation	Additional description: Large intestine perforation		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastritis	Additional description: Gastritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 24 (54.17%)	2 / 7 (28.57%)	
occurrences (all)	27	2	
Submaxillary gland enlargement	Additional description: Submaxillary gland enlargement		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Haemorrhoids	Additional description: Haemorrhoids		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gingival pain	Additional description: Gingival pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Swollen tongue	Additional description: Swollen tongue		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 24 (45.83%)	4 / 7 (57.14%)	
occurrences (all)	17	7	
Diarrhoea	Additional description: Diarrhoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 24 (50.00%)	3 / 7 (42.86%)	
occurrences (all)	20	7	
Angular cheilitis	Additional description: Angular cheilitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspepsia	Additional description: Dyspepsia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 24 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Faeces discoloured	Additional description: Faeces discoloured		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Flatulence	Additional description: Flatulence		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Overflow diarrhoea	Additional description: Overflow diarrhoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort	Additional description: Abdominal discomfort		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Anal fissure	Additional description: Anal fissure		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration	Additional description: Mouth ulceration		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Abdominal mass	Additional description: Abdominal mass		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic steatosis	Additional description: Hepatic steatosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pain of skin	Additional description: Pain of skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis	Additional description: Hyperhidrosis		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Dry skin	Additional description: Dry skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	3 / 7 (42.86%)	
occurrences (all)	1	3	
Erythema	Additional description: Erythema		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Night sweats	Additional description: Night sweats		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rash	Additional description: Rash		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 24 (20.83%)	2 / 7 (28.57%)	
occurrences (all)	5	2	
Skin lesion	Additional description: Skin lesion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Blood blister	Additional description: Blood blister		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin discolouration	Additional description: Skin discolouration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Alopecia	Additional description: Alopecia		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	4	1	

Rash pruritic	Additional description: Rash pruritic		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Skin ulcer	Additional description: Skin ulcer		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Rash macular	Additional description: Rash macular		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nail discolouration	Additional description: Nail discolouration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Nail growth abnormal	Additional description: Nail growth abnormal		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nail dystrophy	Additional description: Nail dystrophy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pruritus	Additional description: Pruritus		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 24 (20.83%)	0 / 7 (0.00%)	
occurrences (all)	8	0	
Eczema	Additional description: Eczema		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Calculus urinary	Additional description: Calculus urinary		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Groin pain	Additional description: Groin pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Myalgia	Additional description: Myalgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Metatarsalgia	Additional description: Metatarsalgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Arthralgia	Additional description: Arthralgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	5	2	
Bone pain	Additional description: Bone pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Pain in extremity	Additional description: Pain in extremity		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	5	0	
Arthritis	Additional description: Arthritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Muscle spasms	Additional description: Muscle spasms		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	2 / 24 (8.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Pain in jaw	Additional description: Pain in jaw		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Neck pain	Additional description: Neck pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Metapneumovirus infection	Additional description: Metapneumovirus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oral candidiasis	Additional description: Oral candidiasis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Rhinitis	Additional description: Rhinitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Cellulitis	Additional description: Cellulitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
COVID-19	Additional description: COVID-19		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 24 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	8	1	
Pneumocystis jirovecii pneumonia	Additional description: Pneumocystis jirovecii pneumonia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Herpes zoster	Additional description: Herpes zoster		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Oral herpes	Additional description: Oral herpes		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nail bed infection	Additional description: Nail bed infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Influenza	Additional description: Influenza		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eye infection	Additional description: Eye infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	2 / 7 (28.57%)	
occurrences (all)	1	3	
Wound infection	Additional description: Wound infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nasopharyngitis	Additional description: Nasopharyngitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gingivitis	Additional description: Gingivitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Helicobacter gastritis	Additional description: Helicobacter gastritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Neutropenic sepsis	Additional description: Neutropenic sepsis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia	Additional description: Hypokalaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Decreased appetite	Additional description: Decreased appetite		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	4	2	
Hypoalbuminaemia	Additional description: Hypoalbuminaemia		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 24 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vitamin B12 deficiency	Additional description: Vitamin B12 deficiency		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Folate deficiency	Additional description: Folate deficiency		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2017	v1 - Addition of patient cards.
20 December 2017	v3 - Updated editions of investigator brochure for R-CHOP and Acalabrutinib. Updates to inclusion and exclusion criteria to add clarification. Tumour block hierarchy of testing clarified. List of prohibited proton pump inhibitors added as an appendix. Updated patient information sheets to detail prohibited medications.
11 July 2018	v4 - Updated editions of investigator brochure for acalabrutinib. Clarification of PET-CT requirements and permitted time windows for assessments in the protocol. Introduction of a centralised review of signed consent forms at the SCTU via nhs.net email. Introduction of a Tissue Block Screening Information Sheet and Consent Form to enable patient's diagnostic tissue sample to be sent to HMDS in Leeds (central lab) prior to main study consent. Introduction of a Pregnant Partner Information Sheet and Consent Form. Addition of Pneumocystis jirovecii pneumonia (PCP) prophylaxis to the protocol. Amendments to the protocol and patient information sheets to meet GDPR requirements.
13 December 2018	v5 - Age restriction to exclude patients aged 65 and over introduced in line with urgent safety measure.
04 September 2019	v6 - Reversal of urgent safety measure to include patients aged 65 and over. Updated editions of investigator brochure for acalabrutinib and SmPCs for the components of R-CHOP. Removal of the optional BTK occupancy sub-study. Adverse events to be collected from date of consent. Permitted window introduced for end of treatment and follow up visits, as well as translational samples. Exclusion criteria updated to state patients taking a proton pump inhibitor should be switched to a short-acting H2-receptor antagonist or antacid prior to study entry. Supportive care updated to state GCSF support and infective prophylaxis are mandatory. Dose modification section updated in line with GCSF becoming mandatory. Contraception requirements clarified and a definition of women of childbearing potential added to the protocol. Overdose definition changed and reporting requirements clarified. Warnings and precautions related to acalabrutinib added. Suspected transmission of an infection agent via the study drug and potential drug induced liver injury added to safety reporting requirements. Pregnancy reporting requirements updated and pregnant partners information sheet and consent form amended to apply to both pregnant participants and partners of pregnant participants. Data sharing statement added. Clarification added that bidimensional measurements are expected for CT scans. Discrepancies between text and schedule of observations corrected for baseline blood tests. End of study date updated.
16 December 2020	v9 - Addition of Event-Free Survival and Time To Treatment Failure as secondary endpoints. Clarification of statistical analysis populations.

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.

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33093947