Clinical trial results:
An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis.

Summary

EudraCT number	2012-001102-14
Trial protocol	GB CZ ES SE IT IE
Global end of trial date	29 November 2019

Results information

Result version number	v1 (current)
This version publication date	09 July 2021
First version publication date	09 July 2021

Trial information

Trial identification

Sponsor protocol code	Ritazarem

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01697267
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Carrie Bayliss, Cambridge University Hospitals NHS Foundation Trust, 0044 01223 348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, Cambridge University Hospitals NHS Foundation Trust, 0044 01223 348158, cctu@addenbrookes.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	18 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2019
Global end of trial reached?	Yes
Global end of trial date	29 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of rituximab against azathioprine in the prevention of disease flare in ANCA-associated vasculitis patients with relapsing disease.

Protection of trial subjects:

Trial subjects were carefully monitored for the duration of the study, with frequent visits and follow-up. Treatment administration was in line with their usual standard of care and no additional distress was expected from participation in the trial.

Background therapy: -

Evidence for comparator:

Rationale for the use of rituximab in AAV: B cells play a key role in the pathogenesis of AAV. Not only are they the precursors of ANCA secreting plasma cells, but they also act as antigen presenting cells for autoreactive T cells, providing co-stimulatory support and initiating T cell activation, as well as producing pro-inflammatory cytokines, such as IL-6 and TNFα. Specifically depleting B cells with targeted biological agents, such as rituximab, is therefore a promising approach to the treatment of AAV.

Actual start date of recruitment	19 April 2013
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	Australia: 11
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	188
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	118
From 65 to 84 years	69
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

RITAZAREM is a joint venture of the European Vasculitis Study Group (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC). RITAZAREM was conducted in multiple centres internationally including Europe, North America and Australia/New Zealand and Japan.

Pre-assignment

Screening details:

Patients were evaluated by their local trial investigators to ensure they met all the inclusion criteria and none of the exclusion criteria. The screening visit required confirmation of the diagnosis of AAV (ANCA positivity, current or historical and pertinent histology results) and documentation of organ manifestations of active AAV.

Period 1

Period 1 title	Induction Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open label study. A non-blinded, open label study was been chosen for reasons of simplicity and practicality in view of RITAZAREM being an international multi-centre trial. Previous EUVAS studies with similar end-points have also been unblinded yet have led to robust and reproducible conclusions.

Arms

Arm title	Rituximab induction therapy

Arm description:

Patients were recruited at the time of relapse. All received rituximab 375 mg/m2/week x 4 and glucocorticoids to achieve remission. Those patients that achieved disease control (BVAS/WG ≤ 1 and daily prednisone dose ≤ 10 mg) by month 4 were eligible for the subsequent phase of the trial (phase 2) where they were randomised to either rituximab or control remission maintenance therapy.

Arm type	Induction therapy
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rituxan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were recruited at the time of relapse. All received rituximab 375 mg/m2/week x 4 doses and glucocorticoids.
The first dose of rituximab should have been given within 14 days of enrolment into the trial.
All induction doses of rituximab should have been completed by week 6.
First infusion: the recommended initial infusion rate for rituximab is 50 mg/h; subsequently, the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.
Subsequent infusions: subsequent infusions of rituximab can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.
Pre-medication with 100 mg IV methylprednisolone will be administered prior the first infusion to minimise infusion reactions.
Sites will follow local pre-medication practice for infusions 2, 3, and 4. 100 mg IV methylprednisolone will be administered prior to each maintenance dose.

Number of subjects in period 1	Rituximab induction therapy
Started	188
Completed	170
Not completed	18
Adverse event, serious fatal	4
Consent withdrawn by subject	3
Physician decision	2
Missed randomisation window	1
Lost to follow-up	1
Not eligible for induction therapy	1
Not in remission at month 4	6

Period 2

Period 2 title	Maintenance Phase
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open label study. A non-blinded, open label study has been chosen for reasons of simplicity and practicality in view of RITAZAREM being an international multi-centre trial. Previous EUVAS studies with similar end-points have also been unblinded yet have led to robust and reproducible conclusions.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab maintenance tharapy

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rituxan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 1000 mg x 1 dose at months 4, 8, 12, 16 and 20 and glucocorticoids.

Arm title	Azathioprine

Arm description:

Control maintenance therapy

Arm type	Active comparator

Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the control arm will receive oral azathioprine, to be taken daily. The maximum daily dose allowed is 200mg.
The maximum treatment period is 27 months, with tapering at month 24 as described below.
The target dose is 2mg/kg. The maximum daily dose is 200mg.
This should be continued until month 24. The dose should then be reduced by 50% and azathioprine completely withdrawn at month 27.
The dose should be rounded down to the nearest 25mg. The dose may vary on alternate days e.g. 100mg.
Methotrexate or mycophenolate mofetil were permitted for those individuals intolerant of azathioprine. Methotrexate 25 mg/week will be substituted for patients with GFR > 50 ml/min and intolerant of azathioprine even at a reduced dose of 1 mg/kg/day. Mycophenolate mofetil 2 g/day will be substituted for patients intolerant of azathioprine and with GFR < 50 ml/min, and glucocorticoids. Intolerance is defined as the occurrence of an adverse event.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The protocol comprises an induction phase (period 1) and a maintenance phase (period 2). During the induction period, all patients receive the same treatment to bring the disease under remission, only the patients who achieve remission by month 4 are entered in the randomised second phase of the trial, which aims to assess the efficacy of rituximab compared to azathioprine in the prevention of disease relapse in AAV patients with relapsing disease.

Number of subjects in period 2[2]	Rituximab	Azathioprine
Started	85	85
Month 24	78	78
Completed	71	70
Not completed	14	15
Adverse event, serious fatal	3	1
Consent withdrawn by subject	5	5
Physician decision	-	4
Adverse event, non-fatal	2	2
Lost to follow-up	4	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The total number of patients enrolled in the trial comprises all patients enrolled in the induction phase of the trial (phase 1) while only those who achieved disease remission by month 4 are entered in the randomisad maintenance phase of the trial (phase 2). Baseline is taken to be at the point of randomisation (month 4) and encompass only those patients who achieve disease remission by month 4.

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
Rituximab maintenance tharapy	
Reporting group title	Azathioprine
Reporting group description:	
Control maintenance therapy	

Reporting group values	Rituximab	Azathioprine	Total
Number of subjects	85	85	170
Age categorical			
Age at baseline			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	51	105
From 65-84 years	30	34	64
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	57.1	58.6	
standard deviation	± 15.1	± 13.9	-
Gender categorical			
Units: Subjects			
Female	42	44	86
Male	43	41	84
Race			
Units: Subjects			
White	78	77	155
Black	0	0	0
Asian	5	5	10
Hispanic	2	1	3
Other	0	2	2
Induction regimen			
Glucocorticoids during the induction phase. Selected prednisone induction regimen (1A or 1B). Induction Schedule A: 1 mg/kg. Induction Schedule B: 0.5 mg/kg.			
Units: Subjects			
1A	24	24	48
1B	61	61	122
ANCA type			
Units: Subjects			
anti-PR3	61	62	123

anti-MPO	24	23	47
Relapse type Units: Subjects			
Severe	52	54	106
Non-severe	33	31	64
Historical ANCA positivity			
Historical positivity to anti-PR3 and/or anti-MPO as declared at enrolment.			
Units: Subjects			
anti-MPO	23	22	45
anti-PR3	61	61	122
Both	0	2	2
Neither	1	0	1
Comorbidities: Hypertension Units: Subjects			
Yes	41	45	86
No	44	40	84
Unknwon	0	0	0
Comorbidities: Ischemic Heart Disease (IHD) Units: Subjects			
Yes	7	1	8
No	78	83	161
Unknown	0	1	1
Comorbidities: Chronic Lung Disease (COPD) Units: Subjects			
Yes	11	13	24
No	74	72	146
Unknown	0	0	0
Comorbidities: Cerebro-Vascular Disease (CVD) Units: Subjects			
Yes	3	2	5
No	82	83	165
Unknown	0	0	0
Comorbidities: Cancer Units: Subjects			
Yes	12	7	19
No	73	78	151
Unknown	0	0	0
Comorbidities: Venus Thromboembolism Units: Subjects			
Yes	10	10	20
No	75	75	150
Unknown	0	0	0
Comorbidities: Diabetes Units: Subjects			
Yes	6	13	19
No	78	72	150
Unknown	1	0	1
Historical Organ Involvement: Constitutional Symptom			

Units: Subjects			
Yes	43	48	91
No	42	37	79
Historical Organ Involvement: Joints Units: Subjects			
Yes	58	67	125
No	27	18	45
Historical Organ Involvement: Skin Units: Subjects			
Yes	27	27	54
No	58	58	116
Historical Organ Involvement: Mucous Membranes/Eyes Units: Subjects			
Yes	28	30	58
No	57	55	112
Historical Organ Involvement: Ear/Nose/Throat Units: Subjects			
Yes	67	60	127
No	18	25	43
Historical Organ Involvement: Heart Units: Subjects			
Yes	3	3	6
No	82	82	164
Historical Organ Involvement: Gastrointestinal Tract Units: Subjects			
Yes	1	2	3
No	84	83	167
Historical Organ Involvement: Lungs Units: Subjects			
Yes	52	51	103
No	33	34	67
Historical Organ Involvement: Kidneys Units: Subjects			
Yes	57	57	114
No	28	28	56
Historical Organ Involvement: Nervous System Units: Subjects			
Yes	27	20	47
No	58	65	123
Historical Organ Involvement: Other Units: Subjects			
Yes	18	22	40
No	67	63	130
Total number of Body Systems Units: Subjects			
One (1)	3	4	7
Two (2)	7	9	16
Three (3)	12	12	24

Four (4)	20	11	31
Five (5)	18	23	41
Six (6)	14	16	30
Seven (7)	7	8	15
Eight (8)	2	1	3
Nine (9)	1	0	1
Ten (10)	0	1	1
Zero (0)	1	0	1
Prior Treatments: Methylprednisolone Units: Subjects			
Yes	63	64	127
No	22	21	43
Prior Treatments: Predniso(lo)ne Units: Subjects			
Yes	83	85	168
No	2	0	2
Prior Treatments: Oral Cyclophosphamide Units: Subjects			
Yes	32	34	66
No	53	51	104
Prior Treatments: IV Cyclophosphamide Units: Subjects			
Yes	41	43	84
No	44	42	86
Prior Treatments: Cyclophosphamide (any) Units: Subjects			
Yes	67	66	133
No	18	19	37
Prior Treatments: Rituximab Units: Subjects			
Yes	33	27	60
No	52	58	110
Prior Treatments: Azathioprine Units: Subjects			
Yes	66	60	126
No	19	25	44
Prior Treatments: Methotrexate Units: Subjects			
Yes	32	24	56
No	53	61	114
Prior Treatments: Mycophenolate Mofetil Units: Subjects			
Yes	21	22	43
No	64	63	127
Prior Treatments: Sulfamethoxazole/Trimethoprim Units: Subjects			
Yes	32	31	63
No	53	54	107
Prior Treatments: Plasma Exchange			

Units: Subjects			
Yes	13	11	24
No	72	74	146
Prior Treatments: IVIG Units: Subjects			
Yes	2	3	5
No	83	82	165
Prior Treatments: anti-TNFs Units: Subjects			
Yes	0	2	2
No	85	83	168
Prior Treatments: Other immunosuppression Units: Subjects			
Yes	4	6	10
No	81	79	160
Number of prior immunosuppressants (excluding glucocorticoids)			
A count of the number of prior immunosuppressants (excluding glucocorticoids) received by each subject. The following treatments are included: cyclophosphamide (Oral or IV), rituximab, azathioprine, methotrexate, mycophenolate mefotil, IVIG, anti-TNFs, and other immunosuppression listed in the Baseline Medical History Form. In incomplete cases, the subject will be regarded as not having received the treatment specified.			
Units: Subjects			
Zero (0)	0	0	0
One (1)	11	11	22
Two (2)	32	43	75
Three (3)	25	17	42
Four (4)	12	10	22
Five (5)	2	2	4
Six (6)	3	1	4
Seven (7)	0	0	0
Eight (8)	0	0	0
Nine (9)	0	1	1
Weight Units: Kg			
arithmetic mean	86.6	86	
standard deviation	± 23.9	± 25.3	-
Height Units: cm			
arithmetic mean	171	170	
standard deviation	± 11	± 9.95	-
Body Surface Area Units: m2			
arithmetic mean	1.98	1.96	
standard deviation	± 0.278	± 0.275	-
Rituximab induction dose (mg/infusion) Units: mg			
arithmetic mean	743	734	
standard deviation	± 104.1	± 101.9	-
Disease duration			
Prior disease duration (years) - calculated from the date of diagnosis to the date of screening.			
Units: years			

arithmetic mean	7.38	6.93	
standard deviation	± 6.94	± 6.10	-
Total number of Body Systems affected			
The total count of organ manifestations reported in the Baseline Medical History Form (max count = 11), the organ systems are: Constitutional Symptom, Joints, Skin, Mucous Membranes/Eyes, Ear/Nose/Throat, Heart, Gastrointestinal Tract, Lungs, Kidneys, Nervous System, Other.			
Units: counts			
arithmetic mean	4.48	4.55	
standard deviation	± 1.75	± 1.79	-
Prior Treatments (Doses): Rituximab			
Units: gram(s)			
arithmetic mean	4466	5403	
standard deviation	± 2945	± 3573	-
Prior Treatments (Doses): Oral Cyclophosphamide			
Units: gram(s)			
arithmetic mean	46.9	41.3	
standard deviation	± 70.8	± 42.3	-
Prior Treatments (Doses): IV Cyclophosphamide			
Units: gram(s)			
arithmetic mean	7.28	9.05	
standard deviation	± 6.12	± 8.42	-
Prior Treatments (Doses): Total Cyclophosphamide			
Units: gram(s)			
arithmetic mean	24.4	26.9	
standard deviation	± 50.4	± 35.5	-
Number of prior immunosuppressants (excluding glucocorticoids)			
A count of the number of prior immunosuppressants (excluding glucocorticoids) received by each subject. The following treatments are included: cyclophosphamide (Oral or IV), rituximab, azathioprine, methotrexate, mycophenolate mefotil, IVIG, anti-TNFs, and other immunosuppression listed in the Baseline Medical History Form. In incomplete cases, the subject will be regarded as not having received the treatment specified.			
Units: subjects			
arithmetic mean	2.66	2.51	
standard deviation	± 1.16	± 1.24	-

End points

End points reporting groups

Reporting group title	Rituximab induction therapy

Reporting group description:

Patients were recruited at the time of relapse. All received rituximab 375 mg/m2/week x 4 and glucocorticoids to achieve remission. Those patients that achieved disease control (BVAS/WG ≤ 1 and daily prednisone dose ≤ 10 mg) by month 4 were eligible for the subsequent phase of the trial (phase 2) where they were randomised to either rituximab or control remission maintenance therapy.

Reporting group title	Rituximab

Reporting group description:

Rituximab maintenance tharapy

Reporting group title	Azathioprine

Reporting group description:

Control maintenance therapy

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population comprises all consented subjects enrolled in the trial, regardless of whether they achieved remission and were randomised at month 4. The treatment group will be analysed as randomised (rituximab or azathioprine), patients who were enrolled but not randomised will be classified as belonging to the induction group (induction).

Subject analysis set title	Maintenance compliant
Subject analysis set type	Per protocol

Subject analysis set description:

This per-protocol populations includes all randomised patients who have not deviated from protocolised treatment during the maintenance phase of the trial (from randomisation to month 24). Patients who withdraw from trial or from protocolised treatment will be assessed for compliance up to the point of their withdrawal.

Subject analysis set title	Follow-up compliant
Subject analysis set type	Per protocol

Subject analysis set description:

This per-protocol populations includes all randomised patients who have not deviated from protocolised treatment during the follow-up (from randomisation to end of trial). It is assumed that maintenance compliance is necessary for follow-up compliance. Patients who withdraw from trial or from protocolised treatment will be assessed for compliance up to the point of their withdrawal.

Primary: First Major or Minor Relapse

End point title	First Major or Minor Relapse

End point description:

The primary efficacy outcome measure of the trial is relapse-free survival, where a relapse is either major or minor. The primary analysis is a Cox regression model adjusted for the stratification factors (ANCA type, relapse severity and prednisone induction regimen) for the difference in the distribution of relapse-free survival between the rituximab arm and the azathioprine (control) arm (two-sided at α-level of 5%). Assuming a proportional hazard holds, the hazard ratio together with the 95% confidence interval will be estimated using a Cox regression model adjusted for the stratification factors.

End point type	Primary

End point timeframe:

Patients are followed up from a mimumum of 36 months to a maximum of 48 months from enrolment (month 0). The primary endpoint is time to disease relapse (either minor or major relapse) from randomisation (month 4).

End point values	Rituximab	Azathioprine	Maintenance compliant	Follow-up compliant
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	85	85	159	145
Units: subjects	38	60	94	79

Attachments (see zip file)	by Treatment and Induction Regimen/fig_8.02.2.png First Major or Minor Relapse - Kaplan-Meier Plot/fig_8.02.1.png by Treatment and ANCA status/fig_8.02.3.png by Treatment and Relapse Type/fig_8.02.4.png Hazard Ratios/fig_8.05.2.png

Statistical analyses

Statistical analysis title	Cox regression model (all time points)

Statistical analysis description:

A Cox regression model adjusted for the stratification factors (ANCA type, relapse severity and prednisone induction regimen) for the difference in the distribution of relapse-free survival between the rituximab arm and the azathioprine (control) arm (two-sided at α-level of 5%).

Comparison groups	Rituximab v Azathioprine
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.21

Statistical analysis title	Cox regression model (during treatment)

Statistical analysis description:

There will be a closed testing procedure, first the null hypothesis will be teste for a hazard ratio of 1 at all time points. If this is rejected at a 5% level then two further sub-hypothesis will be examined using time-varying covariates:
1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).
2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post treatment).

Comparison groups	Rituximab v Azathioprine

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.001 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.66
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[1] - Following the closed testing procedure this analysis is carried out because the null hypothesis at all time points has been rejected at 5% level.
[2] - 1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).

Statistical analysis title	Cox regression model (post treatment)

Statistical analysis description:

There will be a closed testing procedure, first the null hypothesis will be teste for a hazard ratio of 1 at all time points. If this is rejected at a 5% level then two further sub-hypothesis will be examined using time-varying covariates:
1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).
2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post treatment).

Comparison groups	Rituximab v Azathioprine
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.004 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.78
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[3] - Following the closed testing procedure this analysis is carried out because the previous null hypothesis at all time points and during treatment have been rejected at 5% level.
[4] - 2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post treatment)

Secondary: Major or Second Minor Relapse

End point title	Major or Second Minor Relapse

End point description:

Time to a major or second minor relapse.

End point type	Secondary

End point timeframe:

Patients are followed up from a mimumum of 36 months to a maximum of 48 months from enrolment (month 0). The primary endpoint is time to disease relapse (either minor or major relapse) from

randomisation (month 4).

End point values	Rituximab	Azathioprine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	85		
Units: subjects	16	40		

Attachments (see zip file)	Major or Second Minor Relapse - Kaplan-Meier Plot/fig_9.02.1. Cox Proportional Hazards Model/fig_9.05.2.png

Statistical analyses

Statistical analysis title	Cox regression model (all time points)

Statistical analysis description:

A Cox regression model adjusted for the stratification factors (ANCA type, relapse severity and prednisone induction regimen) for the difference in the distribution of relapse-free survival between the rituximab arm and the azathioprine (control) arm (two-sided at α-level of 5%).

Comparison groups	Rituximab v Azathioprine
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Cox regression model (during treatment)

Statistical analysis description:

There will be a closed testing procedure, first the null hypothesis will be teste for a hazard ratio of 1 at all time points. If this is rejected at a 5% level then two further sub-hypothesis will be examined using time-varying covariates:
1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).
2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post treatment).

Comparison groups	Rituximab v Azathioprine

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.008 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.72
Variability estimate	Standard error of the mean
Dispersion value	0.47

Notes:

[5] - Following the closed testing procedure this analysis is carried out because the null hypothesis at all time points has been rejected at 5% level.
[6] - 1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).

Statistical analysis title	Copy of Cox regression model (post treatment)

Statistical analysis description:

There will be a closed testing procedure, first the null hypothesis will be teste for a hazard ratio of 1 at all time points. If this is rejected at a 5% level then two further sub-hypothesis will be examined using time-varying covariates:
1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).
2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post treatment).

Comparison groups	Rituximab v Azathioprine
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.006 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[7] - Following the closed testing procedure this analysis is carried out because the previous null hypotheses at all time points and during treatment have been rejected at 5% level.
[8] - 2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post treatment)

Other pre-specified: Remission at month 4

End point title	Remission at month 4

End point description:

This analysis will report on the four month open-label induction phase of the trial. It will address the efficacy of rituximab at re-inducing remission in patients with ANCA-associated vasculitis who have relapsed.

End point type	Other pre-specified

End point timeframe:

The induction phase of the trial covers the first four month, from enrolment to month 4 inclusive. In this period all patients receive the same treatment (rituximab induction therapy) aimed at re-introducing remission.

End point values	Rituximab induction therapy			
Subject group type	Reporting group			
Number of subjects analysed	188			
Units: subjects				
In remission	171			
Not in remission	17			

Attachments (see zip file)	BVAS/WG - Disease Status/fig_4.02.5.png

Statistical analyses

No statistical analyses for this end point

Post-hoc: Major Relapse

End point title	Major Relapse

End point description:

Time to a major relapse.

End point type	Post-hoc

End point timeframe:

Patients are followed up from a mimumum of 36 months to a maximum of 48 months from enrolment (month 0). The primary endpoint is time to disease relapse (either minor or major relapse) from randomisation (month 4).

End point values	Rituximab	Azathioprine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	85		
Units: subjects	11	26		

Attachments (see zip file)	Kaplan-Meier Plot - Major Relapse/fig_10.02.1.png Cox Proportional Hazards Model - Forest Plot/fig_10.05.2.png

Statistical analyses

Statistical analysis title	Cox regression model (all time points)

Statistical analysis description:

A Cox regression model adjusted for the stratification factors (ANCA type, relapse severity and prednisone induction regimen) for the difference in the distribution of relapse-free survival between the rituximab arm and the azathioprine (control) arm (two-sided at α-level of 5%).

Comparison groups	Rituximab v Azathioprine
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.73
Variability estimate	Standard error of the mean
Dispersion value	0.36

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs recorded from enrollment until the end of the trial, thus events reported both during the induction and maintenance phase of the trial are reported. Reporting groups (Induction, Rituximab, Azathioprine) refer to the patient's assigned treatment group.

Adverse event reporting additional description:

In addition to all SAEs, the following selected adverse events are reported:
infections (all episodes requiring IV treatment or oral antibiotics);
AEs resulting in a change in dose of trial IMPs, or the addition of relevant concomitant medication, or the occurrance of a lab abnormality;
new malignancies.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Rituximab
Reporting group description: -	
Reporting group title	Induction
Reporting group description: -	
Reporting group title	Azathioprine

Reporting group description: -

Serious adverse events	Rituximab	Induction	Azathioprine
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 85 (50.59%)	11 / 18 (61.11%)	48 / 85 (56.47%)
number of deaths (all causes)	3	5	1
number of deaths resulting from adverse events	3	5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal squamous cell carcinoma	Additional description: Anal squamous cell carcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma	Additional description: B-cell lymphoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Bladder papilloma	Additional description: Bladder papilloma		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colon neoplasm	Additional description: Colon neoplasm		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung adenocarcinoma	Additional description: Lung adenocarcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatic carcinoma metastatic	Additional description: Pancreatic carcinoma metastatic		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1

Pancreatic carcinoma	Additional description: Pancreatic carcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Sarcoma of skin	Additional description: Sarcoma of skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection	Additional description: Aortic dissection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis	Additional description: Deep vein thrombosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 85 (4.71%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis	Additional description: Epistaxis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis	Additional description: Haemoptysis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage	Additional description: Haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension	Additional description: Orthostatic hypotension		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism	Additional description: Pulmonary embolism		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular injury	Additional description: Vascular injury		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm	Additional description: Vascular pseudoaneurysm		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Aortic valve replacement	Additional description: Aortic valve replacement		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bunion operation	Additional description: Bunion operation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ablation	Additional description: Cardiac ablation		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy	Additional description: Cholecystectomy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colostomy closure	Additional description: Colostomy closure		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colporrhaphy	Additional description: Colporrhaphy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryocystorhinostomy	Additional description: Dacryocystorhinostomy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty	Additional description: Hip arthroplasty		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion	Additional description: Infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Joint resurfacing surgery	Additional description: Joint resurfacing surgery		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty	Additional description: Knee arthroplasty		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung lobectomy	Additional description: Lung lobectomy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and pancreas transplant	Additional description: Renal and pancreas transplant		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal transplant	Additional description: Renal transplant		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sigmoidectomy	Additional description: Sigmoidectomy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal resection	Additional description: Small intestinal resection		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal decompression	Additional description: Spinal decompression		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroidectomy	Additional description: Thyroidectomy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular anastomosis	Additional description: Vascular anastomosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforated ulcer	Additional description: Perforated ulcer		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia	Additional description: Pyrexia		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenosis	Additional description: Stenosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity	Additional description: Drug hypersensitivity		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity	Additional description: Hypersensitivity		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary vasculitis	Additional description: Pulmonary vasculitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis	Additional description: Vasculitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 85 (4.71%)	3 / 18 (16.67%)	9 / 85 (10.59%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm	Additional description: Bronchospasm		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea	Additional description: Dyspnoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal stenosis	Additional description: Laryngeal stenosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum	Additional description: Pneumomediastinum		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis	Additional description: Pneumonitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax	Additional description: Pneumothorax		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor	Additional description: Stridor		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Conversion disorder	Additional description: Conversion disorder		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Medical observation	Additional description: Medical observation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased	Additional description: Transaminases increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accident	Additional description: Accident		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall	Additional description: Fall		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage	Additional description: Intra-abdominal haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication	Additional description: Post procedural complication		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma	Additional description: Subdural haematoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access complication	Additional description: Vascular access complication		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence	Additional description: Wound dehiscence		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome	Additional description: Acute coronary syndrome		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction	Additional description: Acute myocardial infarction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation	Additional description: Atrial fibrillation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete	Additional description: Atrioventricular block complete		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest	Additional description: Cardiac arrest		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive	Additional description: Cardiac failure congestive		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy	Additional description: Cardiomyopathy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Coronary artery disease	Additional description: Coronary artery disease		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction	Additional description: Myocardial infarction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident	Additional description: Cerebrovascular accident		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhagic stroke	Additional description: Haemorrhagic stroke		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome	Additional description: Sleep apnoea syndrome		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage	Additional description: Subdural haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia	Additional description: Iron deficiency anaemia		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia	Additional description: Neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Periorbital oedema	Additional description: Periorbital oedema		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis	Additional description: Colitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer	Additional description: Duodenal ulcer		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula	Additional description: Enterovesical fistula		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal haemorrhage	Additional description: Gastrointestinal haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated	Additional description: Inguinal hernia strangulated		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation	Additional description: Intestinal perforation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	2 / 18 (11.11%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal spasm	Additional description: Oesophageal spasm		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis	Additional description: Oesophagitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis	Additional description: Pancreatitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Small intestinal obstruction	Additional description: Small intestinal obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute	Additional description: Cholecystitis acute		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis	Additional description: Cholelithiasis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula	Additional description: Enterovesical fistula		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis	Additional description: Nephrolithiasis		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria	Additional description: Proteinuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment	Additional description: Renal impairment		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis	Additional description: Myasthenia gravis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis crisis	Additional description: Myasthenia gravis crisis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis	Additional description: Osteoarthritis		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture	Additional description: Pubis fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection	Additional description: Abdominal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis	Additional description: Appendicitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis	Additional description: Bronchitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis	Additional description: Cellulitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective	Additional description: Cholecystitis infective		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection	Additional description: Corona virus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corynebacterium infection	Additional description: Corynebacterium infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryocystitis	Additional description: Dacryocystitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis	Additional description: Diverticulitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection	Additional description: Escherichia urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	1 / 18 (5.56%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	2 / 2	4 / 4	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Escherichia coli	Additional description: Gastroenteritis Escherichia coli		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis viral	Additional description: Gastroenteritis viral		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes zoster	Additional description: Herpes zoster		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes zoster meningoencephalitis	Additional description: Herpes zoster meningoencephalitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infective exacerbation of chronic obstructive airways disease	Additional description: Infective exacerbation of chronic obstructive airways disease		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza	Additional description: Influenza		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	4 / 4	0 / 0	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metapneumovirus infection	Additional description: Metapneumovirus infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes	Additional description: Oral herpes		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital abscess	Additional description: Periorbital abscess		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis	Additional description: Peritonitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia	Additional description: Pneumonia		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 85 (7.06%)	3 / 18 (16.67%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	8 / 8	6 / 7	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral	Additional description: Pneumonia cytomegaloviral		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus	Additional description: Pneumonia haemophilus		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia klebsiella	Additional description: Pneumonia klebsiella		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal	Additional description: Pneumonia pneumococcal		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal	Additional description: Pneumonia pseudomonal		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal	Additional description: Pneumonia staphylococcal		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal	Additional description: Pneumonia streptococcal		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral	Additional description: Pneumonia viral		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection	Additional description: Postoperative wound infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multifocal leukoencephalopathy	Additional description: Progressive multifocal leukoencephalopathy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection	Additional description: Pseudomonas infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection	Additional description: Respiratory syncytial virus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection	Additional description: Respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	4 / 18 (22.22%)	7 / 85 (8.24%)
occurrences causally related to treatment / all	4 / 4	7 / 9	9 / 10
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Sepsis	Additional description: Sepsis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia infection	Additional description: Serratia infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis	Additional description: Sinusitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenotrophomonas infection	Additional description: Stenotrophomonas infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic viral infection	Additional description: Systemic viral infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	2 / 2	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection	Additional description: Viral infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Wound infection	Additional description: Wound infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia	Additional description: Hyperglycaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia	Additional description: Hyperkalaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis	Additional description: Metabolic acidosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Rituximab	Induction	Azathioprine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 85 (70.59%)	7 / 18 (38.89%)	66 / 85 (77.65%)
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 / 85 (1.18%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	1	0	2
Gastrointestinal carcinoma	Additional description: Gastrointestinal carcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Malignant melanoma	Additional description: Malignant melanoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Oesophageal carcinoma	Additional description: Oesophageal carcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Prostate cancer	Additional description: Prostate cancer		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	3 / 85 (3.53%)
occurrences (all)	0	2	5
Investigations			
Streptococcus test positive	Additional description: Streptococcus test positive		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Malaise	Additional description: Malaise		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Eye disorders			

Blepharitis	Additional description: Blepharitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Cheilitis	Additional description: Cheilitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Eczema	Additional description: Eczema		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Rosacea	Additional description: Rosacea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Infections and infestations			
Bacterial dacryocystitis	Additional description: Bacterial dacryocystitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Bacterial infection	Additional description: Bacterial infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Beta haemolytic streptococcal infection	Additional description: Beta haemolytic streptococcal infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Body tinea	Additional description: Body tinea		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Bronchitis	Additional description: Bronchitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Bronchitis haemophilus	Additional description: Bronchitis haemophilus		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	2	0	1
Candida infection	Additional description: Candida infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	1 / 18 (5.56%)	2 / 85 (2.35%)
occurrences (all)	1	1	2
Cellulitis	Additional description: Cellulitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 85 (4.71%)	0 / 18 (0.00%)	5 / 85 (5.88%)
occurrences (all)	4	0	7
Cellulitis orbital	Additional description: Cellulitis orbital		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Citrobacter infection	Additional description: Citrobacter infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	1	0	1
Clostridium difficile infection	Additional description: Clostridium difficile infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0

Conjunctivitis	Additional description: Conjunctivitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	0 / 18 (0.00%)	3 / 85 (3.53%)
occurrences (all)	4	0	3
Cystitis	Additional description: Cystitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Cystitis escherichia	Additional description: Cystitis escherichia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	1	0	4
Cystitis klebsiella	Additional description: Cystitis klebsiella		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Cytomegalovirus colitis	Additional description: Cytomegalovirus colitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Cytomegalovirus infection	Additional description: Cytomegalovirus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Diverticulitis	Additional description: Diverticulitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Ear infection	Additional description: Ear infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 85 (5.88%)	0 / 18 (0.00%)	4 / 85 (4.71%)
occurrences (all)	7	0	6
Enterococcal infection	Additional description: Enterococcal infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Escherichia urinary tract infection	Additional description: Escherichia urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	0 / 18 (0.00%)	4 / 85 (4.71%)
occurrences (all)	7	0	6
Eye infection	Additional description: Eye infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	3 / 85 (3.53%)
occurrences (all)	0	0	5
Folliculitis	Additional description: Folliculitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	2
Gastrointestinal infection	Additional description: Gastrointestinal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Haemophilus infection	Additional description: Haemophilus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	4 / 85 (4.71%)
occurrences (all)	3	0	4
Herpes simplex	Additional description: Herpes simplex		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	0	2
Herpes zoster	Additional description: Herpes zoster		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	1	0	1
Infected skin ulcer	Additional description: Infected skin ulcer		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0

Infection	Additional description: Infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	1	0	2
Klebsiella infection	Additional description: Klebsiella infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	7 / 85 (8.24%)
occurrences (all)	3	0	12
Lung infection	Additional description: Lung infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Mastoiditis	Additional description: Mastoiditis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Oral candidiasis	Additional description: Oral candidiasis		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	1 / 18 (5.56%)	5 / 85 (5.88%)
occurrences (all)	3	1	7
Oral herpes	Additional description: Oral herpes		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	0	2
Otitis media	Additional description: Otitis media		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	0	2
Parasitic gastroenteritis	Additional description: Parasitic gastroenteritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Paronychia	Additional description: Paronychia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Pharyngitis	Additional description: Pharyngitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	2	0	2
Pneumonia	Additional description: Pneumonia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	3	0	1
Pneumonia haemophilus	Additional description: Pneumonia haemophilus		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	4	0	2
Pneumonia klebsiella	Additional description: Pneumonia klebsiella		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Pneumonia pneumococcal	Additional description: Pneumonia pneumococcal		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Pneumonia pseudomonal	Additional description: Pneumonia pseudomonal		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0

Pneumonia staphylococcal	Additional description: Pneumonia staphylococcal		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Prostate infection	Additional description: Prostate infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Proteus infection	Additional description: Proteus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Pseudomonas bronchitis	Additional description: Pseudomonas bronchitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	3	0	3
Pseudomonas infection	Additional description: Pseudomonas infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Respiratory tract infection	Additional description: Respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	25 / 85 (29.41%)	1 / 18 (5.56%)	35 / 85 (41.18%)
occurrences (all)	58	6	73
Respiratory tract infection viral	Additional description: Respiratory tract infection viral		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Root canal infection	Additional description: Root canal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Serratia infection	Additional description: Serratia infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 85 (0.00%)	1 / 18 (5.56%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Sinusitis	Additional description: Sinusitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 85 (17.65%)	3 / 18 (16.67%)	16 / 85 (18.82%)
occurrences (all)	35	4	24
Skin infection	Additional description: Skin infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 85 (5.88%)	0 / 18 (0.00%)	5 / 85 (5.88%)
occurrences (all)	5	0	5
Staphylococcal impetigo	Additional description: Staphylococcal impetigo		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Staphylococcal infection	Additional description: Staphylococcal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 85 (4.71%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	4	0	3
Systemic infection	Additional description: Systemic infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Tinea infection	Additional description: Tinea infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Tinea pedis	Additional description: Tinea pedis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Tonsillitis	Additional description: Tonsillitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0

Tonsillitis bacterial	Additional description: Tonsillitis bacterial		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Tooth abscess	Additional description: Tooth abscess		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	3 / 85 (3.53%)
occurrences (all)	1	0	4
Tooth infection	Additional description: Tooth infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 85 (3.53%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 85 (22.35%)	2 / 18 (11.11%)	22 / 85 (25.88%)
occurrences (all)	23	2	33
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 85 (11.76%)	1 / 18 (5.56%)	8 / 85 (9.41%)
occurrences (all)	13	1	13
Urinary tract infection enterococcal	Additional description: Urinary tract infection enterococcal		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	2	0	1
Vaginal infection	Additional description: Vaginal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Varicella zoster virus infection	Additional description: Varicella zoster virus infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 85 (0.00%)	0 / 18 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Viral infection	Additional description: Viral infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis	Additional description: Vulvovaginal candidiasis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 85 (1.18%)	0 / 18 (0.00%)	2 / 85 (2.35%)
occurrences (all)	2	0	3
Vulvovaginal mycotic infection	Additional description: Vulvovaginal mycotic infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 85 (2.35%)	0 / 18 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2013	New PIS/consent v2.0
12 September 2013	Protocol v 2.0; Consent - Minor assent form v1.1; PROMIS Questionnaire v2.0; PIS/consent v3.0 1) Addition of patient related outcome questionnaire (PROMIS). 2) Change to dosing advice for azathioprine in older patients. There is limited, objective evidence to support dose reduction of azathioprine with age. This is an historic practice, and would risk under-dosing our comparator group in the trial, possibly masking true treatment effects. The safety parameters and monitoring of azathioprine remain unchanged, and are robust to detect any problems early. 3) Simplification of oral prednisolone dosing by conversion from mg/kg/day to mg/day with two weight divisions. The protocol was written to provide 2 prednisolone regimens (0.5mg/kg or 1.0mg/kg) for investigators to 'tailor' according to the severity of disease manifestations of the patient. The maximum daily dose was set at 60mg in week 0. However, due to the enrolment of two patients into the trial with larger than average Body Mass Index, it became necessary to redesign the regimens according to body weight to take account of this. This is also an important safety measure since adverse reactions to high prednisolone doses are well documented. Clarity has been added to the instruction paragraph for treatment of patient relapse during the trial since there was disagreement in the protocol between earlier instructions. This corrects and clarifies the wording. 4) Change of inclusion/exclusion criteria 5) Reference Safety Information change 6) Rewording of the safety section of the protocol 7) Alignment of follow up assessments for non-randomised patients 8) Clarification of Hepatitis B screening to include new safety information
08 May 2014	Addition of 4 new UK sites (applies to Dudley only the other sites did not set up)

17 September 2015	Consent - Minor assent form v2.0; PIS parent/guardian v4.0; PIS/consent v4.0; Protocol v3.0; 1) Clarification of the number of patients that will be randomised The protocol now reads that at least 160 patients will be randomised, to account for the fact that some patients may have been recruited, but not yet reached the 4 month randomisation point when the target of 160 patients is reached, thus allowing them to continue into the maintenance phase of the trial. 2) Clarification of practicalities of trial A section has been added to the synopsis to make clear the three phases of the trial; further details on the minimisation criteria for randomisation have been added; clarification of the process of screening for pregnancy at the baseline visit has been added as well as additional information for investigators in the Republic of Ireland regarding contraception advice; it is now made clear that rituximab, azathioprine, methotrexate and mycophenolate mofetil are all IMPs for the purpose of this study; further detail regarding actions if IgG levels fall to below 3g/l have been added. Reducing dose of MTX and MMF by 50% at month 24 and then complete withdrawal at month 27, to align with azathioprine 3) Re-wording of the primary objective It now reads "To assess the efficacy of rituximab compared to azathioprine in the prevention of disease flare in AAV patients with relapsing disease", rather than "To demonstrate the superiority of rituximab against azathioprine in the prevention of disease flare in AAV patients with relapsing disease" 4) Safety reporting Kim Mynard has replaced Michelle Lewin as trial coordinator, and therefore the reporting contact for SAEs has been updated to reflect this. Section 13 has been re-worded and re-formatted to clarify the reference safety information for the trial and the definition of expected adverse reactions. In addition, several adverse events of interest will now be collected as part of the study.
05 November 2015	Addition of 3 new UK sites (applies to Leicester and East Kent only) Stevenage did not set up
04 February 2016	Amendment to CTA
14 November 2016	Change in PI at Ipswich site
27 June 2017	Change in RSI; Protocol v4.0 1) Safety reporting Section 11 has been updated to include new reference safety information provided in the Azathioprine and Mycophenolate Mofetil SmPCs. Section 13 has been updated to include new reference safety information provided in the Azathioprine and Mycophenolate Mofetil SmPCs relating to adverse effects and pregnancy. Section 13.1.6 has been updated to clarify the definition of RSI for comparators (UK patients only).
26 July 2017	New PIS/consent v5.0
02 August 2017	Change in PI at Ipswich site
19 February 2018	Change of secondary packaging for IMP PR1 (Rituximab) for this trial

04 September 2018	Update to PIS v6.0 and Protocol v5.0 and update to RSI 1) Safety reporting Sections 11 and 13 have been updated to include the monographs for azathioprine, methotrexate and mycophenolate mofetil as reference safety information for Canada. Sections 11 and 13 have been updated to remove text regarding monitoring assessments for azathioprine, methotrexate and mycophenolate mofetil. Section 11 has been updated to include new reference safety information provided in the Methotrexate SmPC. Several minor changes have also been made to the trial documentation.
19 August 2019	Change in PI at Leicester site

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/32581088