Clinical trial results:
A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

Summary

EudraCT number	2016-001121-14
Trial protocol	IE SE DE GB AT CZ NL ES HU DK BE NO FR IT
Global end of trial date	01 November 2019

Results information

Result version number	v2 (current)
This version publication date	14 March 2024
First version publication date	13 December 2021
Version creation reason	• Correction of full data set Following receipt of ClinicalTrials.gov Protocol Registration and Results System (PRS) comments, the Sponsor would like to make some updates to be consistent across both databases.

Trial information

Trial identification

Sponsor protocol code	CL010_168

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ChemoCentryx, Inc
Sponsor organisation address	850 Maude Avenue, Mountain View, California, United States, 94043
Public contact	Clinical trial disclosure, ChemoCentryx, Inc., clinicaltrials@chemocentryx.com
Scientific contact	Clinical trial disclosure, ChemoCentryx, Inc., clinicaltrials@chemocentryx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002023-PIP01-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2019
Global end of trial reached?	Yes
Global end of trial date	01 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of CCX168 (avacopan) to induce and sustain remission in patients with active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), when used in combination with cyclophosphamide followed by azathioprine, or in combination with rituximab.

Protection of trial subjects:

This study was carried out in compliance with the protocol and its amendments, and in accordance with Good Clinical Practice (GCP), as described in the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice 2000 and the United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR including parts 50 and 56 concerning informed consent and IRB regulations). The study was conducted in accordance with local and national regulatory requirements and the Declaration of Helsinki.
Prior to the initiation of any study procedures, each subject or his/her legal guardian read, signed and dated an IEC or IRB approved ICF. The ICF was reviewed and approved by the Sponsor and the Investigator's IEC / IRB prior to initiation of the study and was in compliance with the Declaration of Helsinki, ICH GCP, and US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A). Sample ICFs and sample subject information are retained in the Trial Master File. The original signed ICF was kept on file by the Investigator with the subject's records, and a copy was given to each subject.

Background therapy:

Subjects in both groups (Prednisone and Avacopan) also received either IV or oral cyclophosphamide followed by oral azathioprine, or IV rituximab, as follows:
• IV cyclophosphamide 15 mg/kg IV up to 1.2 g maximum was given on Day 1 and also at the Week 2, 4, 7, 10, and 13 study visits.
- The cyclophosphamide dose was adjusted based on the subject's age, eGFR, and WBC count according to protocol-specified criteria
• Oral cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) was given orally starting on Day 1 and continuing up to the day before Week 15.
- The cyclophosphamide dose was adjusted based on the subject's age, eGFR, and WBC count according to protocol-specified criteria
• IV rituximab on Day 1, and then Weeks 1, 2, and 3 at a dose of 375 mg/m2 at each visit for a total of 4 weekly infusions
- Glucocorticoid pre-medication for the rituximab IV infusions was allowed

Evidence for comparator: -

Actual start date of recruitment	30 December 2016
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	Netherlands: 6
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	331
EEA total number of subjects	182

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	167
From 65 to 84 years	158
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Overall, demographic characteristics were well balanced between treatment groups. Most subjects were White and not Hispanic or Latino. Geographically, most subjects were enrolled at sites in Europe (70.1%), North America (18.1%) and Japan (6.3%). A total of 143 study centers randomized at least 1 subject. The target enrollment was 300 subjects.

Pre-assignment

Screening details:

Of 386 subjects screened, 331 were enrolled in the study and randomized to treatment. Reasons for subjects failing screening included not meeting inclusion/exclusion criteria, withdrawal by subject, AE and other.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This study was double-blind, double-dummy, i.e., placebo capsules were identical in appearance to the avacopan capsules, and prednisone capsules also had matching placebo capsules. To maintain the blind, multiple measures were taken (i.e., randomization code was not accessible to study personnel who had contact with study centers or who were involved in data management and analysis for the duration of the study).

Arms

Are arms mutually exclusive?	Yes
Arm title	Prednisone group

Arm description:

Avacopan-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone

In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing.

Arm type	Active comparator
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

• Avacopan-matching placebo twice daily orally for 52 weeks (364 days)
- Three avacopan-matching placebo capsules in the morning, preferably with food, and three in the evening, preferably with food, approximately 12 hours after the morning dose
• Oral prednisone tapering regimen over 20 weeks (140 days)
- Prednisone 60 mg per day if the subject's body weight was ≥55 kg, or 45 mg per day if the subject's body weight was <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule
- Adolescents who weighed ≤37 kg started at a prednisone dose of 30 mg per day

Arm title	Avacopan group

Arm description:

Avacopan plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo

Arm type	Experimental

Investigational medicinal product name	Avacopan
Investigational medicinal product code	CCX168
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

• Avacopan 30 mg twice daily orally for 52 weeks (364 days)
- Three 10 mg avacopan capsules in the morning, preferably with food, and three in the evening, preferably with food, approximately 12 hours after the morning dose
• Oral prednisone-matching placebo tapering regimen over 20 weeks (140 days)
- Prednisone-matching placebo capsules equivalent to 60 mg per day if the subject's body weight was ≥55 kg, or 45 mg per day if the subject's body weight was <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule
- Adolescents who weighed ≤37 kg started at a prednisone-matching placebo dose of 30 mg per day

Number of subjects in period 1	Prednisone group	Avacopan group
Started	165	166
Completed	150	151
Not completed	15	15
Adverse event, serious fatal	4	2
Consent withdrawn by subject	3	6
Physician decision	4	3
Adverse event, non-fatal	2	1
Other	-	1
Lost to follow-up	2	1
Withdrawal by parent/guardian	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Prednisone group
Reporting group description:	
Avacopan-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing.	
Reporting group title	Avacopan group
Reporting group description:	
Avacopan plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo	

Reporting group values	Prednisone group	Avacopan group	Total
Number of subjects	165	166	331
Age categorical 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)	1	2	3
Adults (18-50 years)	28	30	58
Adults (51-64 years)	61	48	109
Adults (65-75 years)	52	62	114
Adults (>75 years)	22	24	46
Not recorded	1	0	1
Gender categorical Units: Subjects			
Female	76	68	144
Male	88	98	186
Not recorded	1	0	1
Race Units: Subjects			
Asian	15	17	32
Black or African American	2	3	5
White	140	138	278
Other	6	8	14
Multiple	1	0	1
Not recorded	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	157	151	308
Unknown	1	1	2
Not Reported	1	7	8
Not recorded	1	0	1

Country Units: Subjects			
Australia	4	10	14
Austria	3	3	6
Belgium	4	6	10
Canada	5	8	13
Czech Republic	7	2	9
Denmark	10	6	16
France	18	22	40
Germany	32	22	54
Italy	2	9	11
Japan	10	11	21
Netherlands	5	1	6
New Zealand	2	2	4
Republic of Ireland	4	4	8
Spain	7	8	15
Sweden	2	5	7
Switzerland	6	4	10
United Kingdom	23	17	40
United States of America	20	26	46
Not recorded	1	0	1
Geographic Region Units: Subjects			
North America	25	34	59
Europe and Rest of World excluding Japan	129	121	250
Japan	10	11	21
Not recorded	1	0	1
ANCA-associated vasculitis Status			
ANCA=anti-neutrophil cytoplasmic autoantibody			
Units: Subjects			
Newly diagnosed	114	115	229
Relapsed	50	51	101
Not recorded	1	0	1
ANCA Positivity			
ANCA=anti-neutrophil cytoplasmic autoantibody			
Units: Subjects			
PR3	70	72	142
MPO	94	94	188
Not recorded	1	0	1
Standard of Care Treatment			
IV=intravenous			
Units: Subjects			
Rituximab	107	107	214
IV Cyclophosphamide	51	51	102
Oral Cyclophosphamide	6	8	14
Not recorded	1	0	1
Type of ANCA-associated vasculitis			
ANCA=anti-neutrophil cytoplasmic autoantibody			
Units: Subjects			

Granulomatosis with polyangiitis (GPA)	90	91	181
Microscopic polyangiitis (MPA)	74	75	149
Not recorded	1	0	1
Age at screening			
In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing. Thus, the figure reported in this group is for a total number of subjects of 164.			
Units: year			
arithmetic mean	60.5	61.2	
standard deviation	± 14.50	± 14.56	-
Age at diagnosis of ANCA-associated Vasculitis			
ANCA=anti-neutrophil cytoplasmic autoantibody In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing. Thus, the figure reported in this group is for a total number of subjects of 164.			
Units: year			
arithmetic mean	59.4	59.8	
standard deviation	± 15.19	± 15.60	-
Duration of ANCA-Associated Vasculitis			
ANCA=anti-neutrophil cytoplasmic autoantibody In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing. Thus, the figure reported in this group is for a total number of subjects of 164.			
Units: month			
arithmetic mean	20.13	22.93	
standard deviation	± 40.473	± 52.464	-
Body Weight			
In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing. Thus, the figure reported in this group is for a total number of subjects of 164.			
Units: kilogram(s)			
arithmetic mean	77.71	76.43	
standard deviation	± 19.335	± 20.254	-
BMI			
BMI=Body Mass Index In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing. Thus, the figure reported in this group is for a total number of subjects of 164.			
Units: kilogram(s)/square meter			
arithmetic mean	26.78	26.72	
standard deviation	± 5.212	± 5.997	-
BVAS Score			
BVAS=Birmingham Vasculitis Activity Score BVAS Entry Criteria (N)*: 1 or more major item: 102/104 3 or more minor items: 142/146 2 renal items of proteinuria and hematuria: 57/60 BVAS Components (N)*: General: 114/111 Cutaneous: 23/24 Mucous Membranes/Eyes: 40/26 Ear Nose and Throat:69/75 Chest: 71/71 Cardiovascular: 3/6 Abdominal: 1/4 Renal + Other (RBC Casts and/or Glomerulonephritis): 134/134 Nervous System: 31/38 *Subjects can appear in more than one category; Prednisone/Avacopan Prednisone group - 1 subject withdrawn for not meeting disease criteria prior to dosing. N=164.			
Units: Number			
arithmetic mean	16.2	16.3	
standard deviation	± 5.69	± 5.87	-

VDI Score			
VDI=Vasculitis Damage Index In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing. In addition, two subjects did not have a baseline VDI Score (one in each treatment group). Thus, the figures reported in the Prednisone and Avacopan groups are for a total number of subjects of 163 and 165, respectively.			
Units: Number			
arithmetic mean	0.7	0.7	
standard deviation	± 1.39	± 1.54	-

End points

End points reporting groups

Reporting group title	Prednisone group
Reporting group description:	
Avacopan-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone In the Prednisone group, one subject was randomized but withdrawn for not meeting disease criteria prior to dosing.	
Reporting group title	Avacopan group
Reporting group description:	
Avacopan plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo	

Primary: Percentage of subjects achieving disease remission at Week 26

End point title	Percentage of subjects achieving disease remission at Week 26
End point description:	
Disease remission at Week 26 was defined as: • Achieving a BVAS of 0 as determined by the Adjudication Committee; • No administration of glucocorticoids given for ANCA-associated vasculitis within 4 weeks prior to Week 26; • No BVAS >0 during the 4 weeks prior to Week 26 (if collected for an unscheduled assessment).	
End point type	Primary
End point timeframe:	
Week 26	

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: percentage of subjects				
number (confidence interval 95%)	70.1 (62.5 to 77.0)	72.3 (64.8 to 78.9)		

Statistical analyses

Statistical analysis title	Comparison between groups
Statistical analysis description:	
The proportion of subjects achieving disease remission at Week 26 and the two-sided 95% confidence intervals (CIs) for the difference in proportions was estimated for the comparison between the avacopan group and the prednisone group. For both the noninferiority and superiority tests, the one-sided P-values are presented. Statistical significance was claimed based on the one-sided type-I error of 0.025.	
Comparison groups	Prednisone group v Avacopan group

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	Summary Score test
Parameter estimate	Common difference in remission rates
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	12.8

Notes:

[1] - Summary Score estimate of the common difference and Miettinen-Nurminen (score) confidence limits for the common difference.
[2] - The non-inferiority null hypothesis (H0) for the primary endpoint was rejected and the alternative hypothesis (H1) that the avacopan group was not inferior to the prednisone group when comparing the remission rate at Week 26 was accepted.

Statistical analysis title	Comparison between groups

Statistical analysis description:

The proportion of subjects achieving disease remission at Week 26 and the two-sided 95% confidence intervals (CIs) for the difference in proportions was estimated for the comparison between the avacopan group and the prednisone group. For both the noninferiority and superiority tests, the one-sided P-values are presented. Statistical significance was claimed based on the one-sided type-I error of 0.025.

Comparison groups	Prednisone group v Avacopan group
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.2387 [4]
Method	Summary Score test
Parameter estimate	Common difference in remission rates
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	12.8

Notes:

[3] - Summary Score estimate of the common difference and Miettinen-Nurminen (score) confidence limits for the common difference.
[4] - The superiority null hypothesis (H0) that the avacopan group was not different from the prednisone group when comparing the remission rate at Week 26 was accepted.

Primary: Percentage of subjects achieving sustained disease remission at Week 52

End point title	Percentage of subjects achieving sustained disease remission at Week 52

End point description:

Sustained remission at Week 52 was defined as:
- Disease remission at Week 26 as defined above;
- Disease remission at Week 52 defined as a BVAS of 0 at Week 52 as determined by the Adjudication Committee and no administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52;
- No disease relapse between Week 26 and Week 52 as determined by the Adjudication Committee.

End point type	Primary

End point timeframe:

Week 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: percentage of subjects				
number (confidence interval 95%)	54.9 (46.9 to 62.6)	65.7 (57.9 to 72.8)		

Statistical analyses

Statistical analysis title	Comparison between groups

Statistical analysis description:

The proportion of subjects achieving sustained disease remission at Week 52, and the two-sided 95% confidence intervals (CIs) for the difference in proportions (avacopan minus prednisone) was estimated for the comparison between the avacopan group and the prednisone group. For both the noninferiority and superiority tests, the one-sided P-values are presented. Statistical significance was claimed based on the one-sided type-I error of 0.025.

Comparison groups	Prednisone group v Avacopan group
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.0001 [6]
Method	Summary Score test
Parameter estimate	Common difference in remission rates
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	22.3

Notes:

[5] - Summary Score estimate of the common difference and Miettinen-Nurminen (score) confidence limits for the common difference.

[6] - The non-inferiority null hypothesis (H0) for the efficacy endpoint was rejected and the alternative hypothesis (H1) that the avacopan group was not inferior to the prednisone group when comparing the sustained remission rate at Week 52 was accepted.

Statistical analysis title	Comparison between groups

Statistical analysis description:

The proportion of subjects achieving sustained disease remission at Week 52, and the two-sided 95% confidence intervals (CIs) for the difference in proportions (avacopan minus prednisone) was estimated for the comparison between the avacopan group and the prednisone group. For both the noninferiority and superiority tests, the one-sided P-values are presented. Statistical significance was claimed based on the one-sided type-I error of 0.025.

Comparison groups	Prednisone group v Avacopan group

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0066 [8]
Method	Summary Score test
Parameter estimate	Common difference in remission rates
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	22.3

Notes:

[7] - Summary Score estimate of the common difference and Miettinen-Nurminen (score) confidence limits for the common difference.
[8] - The superiority alternative hypothesis (H1) that the avacopan group was superior to the prednisone group when comparing the sustained remission rate at Week 52 was accepted.

Secondary: Glucocorticoid-induced toxicity as measured by change from baseline over the first 26 weeks in the GTI

End point title	Glucocorticoid-induced toxicity as measured by change from baseline over the first 26 weeks in the GTI

End point description:

GTI-CWS=Glucocorticoid Toxicity Index Cumulative Worsening Score
GTI-AIS=Glucocorticoid Toxicity Index Aggregate Improvement Score
The Glucocorticoid Toxicity Index (GTI) was developed to score glucocorticoid toxicity. The GTI includes: the Cumulative Worsening Score (CWS) that captures cumulative toxicity, both permanent and transient, over the course of time (serves as a cumulative record of toxicity); and the Aggregate Improvement Score that captures both improvement and worsening of toxicity over time (serves as a record of both improving and worsening toxicity). Both scores range from 0 (best health) to 100 (worst health).

End point type	Secondary

End point timeframe:

Baseline, Week 13 and 26

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[9]	160[10]		
Units: Glucocorticoid Toxicity Index				
least squares mean (standard error)				
GTI-CWS (Week 13)	36.6 (± 3.41)	25.7 (± 3.40)		
GTI-CWS (Week 26)	56.6 (± 3.45)	39.7 (± 3.43)		
GTI-AIS (Week 13)	23.2 (± 3.46)	9.9 (± 3.45)		
GTI-AIS (Week 26)	23.4 (± 3.50)	11.2 (± 3.48)		

Notes:

[9] - Number of subjects analysed at Week 26 was 153.

[10] - Number of subjects analysed at Week 26 was 154.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with BVAS of 0 at Week 4, regardless of whether the subjects received glucocorticoids during this period of time and based on assessment by the blinded AC

End point title	Percentage of subjects with BVAS of 0 at Week 4, regardless of whether the subjects received glucocorticoids during this period of time and based on assessment by the blinded AC

End point description:

BVAS=Birmingham Vasculitis Activity Score
AC=Adjudication Committee
The BVAS form is divided into 9 organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis. The clinician only scores features believed to be due to active vasculitis. Completion of the form provides a numerical score, which ranges from 0 (best health) to 63 (worst health).

End point type	Secondary

End point timeframe:

Week 4

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Percentage of subjects				
number (confidence interval 95%)	68.9 (61.2 to 75.9)	62.7 (54.8 to 70.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline over 52 weeks in health-related quality of life as measured by the domains and component scores of the SF-36v2 and EQ-5D-5L VAS and Index

End point title	Change from baseline over 52 weeks in health-related quality of life as measured by the domains and component scores of the SF-36v2 and EQ-5D-5L VAS and Index

End point description:

SF-36v2: Medical Outcomes Survey Short Form-36 version 2;
EQ-5D-5L: EuroQuality of Life-5 Domains-5 Levels
The SF-36v2 component scores and the EQ-5D-5L VAS score range from 0 (worst health) to 100 (best health). The EQ-5D-5L Index Score ranges from 0 (worst health) to 1 (best health).

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150[11]	154[12]		
Units: Change from baseline				
least squares mean (standard error)				
SF-36v2: Physical Component Score (Week 26)	1.344 (± 0.7432)	4.445 (± 0.7332)		
SF-36v2: Physical Component Score (Week 52)	2.626 (± 0.7505)	4.980 (± 0.7435)		
SF-36v2: Physical Functioning (Week 26)	1.88 (± 1.787)	7.31 (± 1.773)		
SF-36v2: Physical Functioning (Week 52)	4.82 (± 1.809)	9.55 (± 1.790)		
SF-36v2: Role Physical (Week 26)	7.52 (± 2.198)	16.78 (± 2.173)		
SF-36v2: Role Physical (Week 52)	12.27 (± 2.228)	17.12 (± 2.198)		
SF-36v2: Bodily Pain (Week 26)	9.82 (± 2.197)	14.75 (± 2.164)		
SF-36v2: Bodily Pain (Week 52)	11.87 (± 2.220)	16.12 (± 2.185)		
SF-36v2: General Health Perception (Week 26)	-2.89 (± 1.428)	3.12 (± 1.405)		
SF-36v2: General Health Perception (Week 52)	-0.17 (± 1.442)	5.84 (± 1.420)		
SF-36v2: Mental Component Score (Week 26)	3.271 (± 0.8403)	4.849 (± 0.8273)		
SF-36v2: Mental Component Score (Week 52)	4.694 (± 0.8491)	6.394 (± 0.8406)		
SF-36v2: Mental Health (Week 26)	6.84 (± 1.331)	8.29 (± 1.318)		
SF-36v2: Mental Health (Week 52)	9.66 (± 1.347)	10.89 (± 1.337)		
SF-36v2: Role Emotional (Week 26)	1.40 (± 2.183)	7.32 (± 2.158)		
SF-36v2: Role Emotional (Week 52)	4.14 (± 2.212)	9.38 (± 2.181)		
SF-36v2: Social Functioning (Week 26)	11.09 (± 2.037)	14.50 (± 2.002)		
SF-36v2: Social Functioning (Week 52)	13.56 (± 2.059)	18.06 (± 2.030)		
SF-36v2: Vitality (Week 26)	6.42 (± 1.751)	12.03 (± 1.727)		
SF-36v2: Vitality (Week 52)	10.48 (± 1.770)	14.36 (± 1.750)		
EQ-5D-5L VAS Score (Week 26)	5.5 (± 1.39)	9.1 (± 1.38)		
EQ-5D-5L VAS Score (Week 52)	7.1 (± 1.41)	13.0 (± 1.39)		
EQ-5D-5L Index Score (Week 26)	-0.0010 (± 0.01462)	0.0229 (± 0.01438)		
EQ-5D-5L Index Score (Week 52)	-0.0038 (± 0.01471)	0.0474 (± 0.01451)		

Notes:

[11] - The number of subjects analysed varied from 144 to 150 amongst the subcategories specified.

[12] - The number of subjects analysed varied from 147 to 154 amongst the subcategories specified.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects and time to experiencing a relapse after previously achieving remission at Week 26 in the study

End point title	Percentage of subjects and time to experiencing a relapse after previously achieving remission at Week 26 in the study

End point description:

A relapse was defined as occurrence of at least one major item in the BVAS, or three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive visits, after:
(a) having achieved remission at Week 26 (BVAS=0 and no glucocorticoids for ANCA-associated vasculitis within 4 weeks) or
(b) having achieved BVAS=0 at any time during the treatment period
The median time to relapse was not estimable because of small number of relapsed subjects.

End point type	Secondary

End point timeframe:

Week 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: percentage of subjects				
number (confidence interval 95%)	12.2 (6.8 to 19.6)	7.5 (3.5 to 13.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: In subjects with renal disease at baseline (based in the BVAS renal component), the change in eGFR from baseline over 52 weeks

End point title	In subjects with renal disease at baseline (based in the BVAS renal component), the change in eGFR from baseline over 52 weeks

End point description:

Change from baseline in kidney function, as measured by eGFR (based on the MDRD equation), was measured in subjects with renal disease based on the BVAS renal component.
eGFR=estimated glomerular filtration rate;
BVAS=Birmingham Vasculitis Activity Score;
MDRD=Modification of Diet in Renal Disease

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[13]	121[14]		
Units: Change in eGFR (mL/min/1.73 m2)				
least squares mean (confidence interval 95%)				

Week 26	2.9 (0.9 to 4.9)	5.8 (3.7 to 7.8)		
Week 52	4.1 (2.1 to 6.1)	7.3 (5.2 to 9.4)		

Notes:

[13] - Number of subjects analysed at Week 52 was 125

[14] - Number of subjects analysed at Week 52 was 119

Statistical analyses

No statistical analyses for this end point

Secondary: In subjects with renal disease and albuminuria at baseline (based in the BVAS renal component), the percent change in UACR from baseline over 52 weeks

End point title	In subjects with renal disease and albuminuria at baseline (based in the BVAS renal component), the percent change in UACR from baseline over 52 weeks

End point description:

BVAS=Birmingham Vasculitis Activity Score;
UACR=Urinary albumin:creatinine ratio

End point type	Secondary

End point timeframe:

Baseline, Week 4, 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[15]	121[16]		
Units: percent change				
least squares mean (confidence interval 95%)				
Week 4	0 (-16 to 19)	-40 (-50 to -28)		
Week 26	-70 (-75 to -65)	-63 (-69 to -56)		
Week 52	-77 (-81 to -72)	-74 (-78 to -69)		

Notes:

[15] - Number of subjects analysed at Week 26 was 118. Number of subjects analysed at Week 52 was 114.

[16] - Number of subjects analysed at Week 26 was 113. Number of subjects analysed at Week 52 was 109

Statistical analyses

No statistical analyses for this end point

Secondary: In subjects with renal disease at baseline (based in the BVAS renal component), the percent change in urinary MCP-1:creatinine ratio from baseline over 52 weeks

End point title	In subjects with renal disease at baseline (based in the BVAS renal component), the percent change in urinary MCP-1:creatinine ratio from baseline over 52 weeks

End point description:

BVAS=Birmingham Vasculitis Activity Score;

MCP-1=monocyte chemoattractant protein-1

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[17]	106[18]		
Units: percent change				
least squares mean (confidence interval 95%)				
Week 26	-64 (-67 to -59)	-67 (-70 to -63)		
Week 52	-71 (-74 to -67)	-73 (-76 to -70)		

Notes:

[17] - Number of subjects analysed at Week 52 was 108.

[18] - Number of subjects analysed at Week 52 was 106.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the VDI from baseline over 52 weeks, including the Week 26 and Week 52 time points

End point title	Change in the VDI from baseline over 52 weeks, including the Week 26 and Week 52 time points

End point description:

VDI=Vasculitis Damage Index
The VDI is comprised of 64 items of damage, grouped into 11 organ-based systems or categorizations. Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity. Damage is also defined as having been present or currently present for at least 3 months. Completion of the form provides a numerical score, which ranges from 0 (best health) to 64 (worst health).

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[19]	161[20]		
Units: score on a scale				
least squares mean (standard error)				
Week 26	0.97 (± 0.092)	1.06 (± 0.090)		
Week 52	1.15 (± 0.093)	1.17 (± 0.091)		

Notes:

[19] - Number of subjects analysed at Week 52 was 151.

[20] - Number of subjects analysed at Week 52 was 150.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject incidence of treatment-emergent SAEs, AEs, and withdrawals due to AEs

End point title	Subject incidence of treatment-emergent SAEs, AEs, and withdrawals due to AEs

End point description:

AEs=Adverse events;
SAEs=Serious adverse events;
TEAE=Treatment-emergent adverse event

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 421/week 60)

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Number				
Number of subjects with at least one TEAE	161	164		
Number of TEAEs	2139	1779		
Number of subjects with SAEs	74	70		
Number of SAEs	166	116		
Subjects with TEAE leading to discontinuation	28	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant ECG changes from baseline

End point title	Number of subjects with clinically significant ECG changes from baseline

End point description:

Clinical significance was assessed by the individual reading of the ECGs.
ECG=Electrocardiogram

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 421/week 60)

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Subjects	8	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects where a relationship between Avacopan/Placebo, glucocorticoid use, cyclophosphamide, rituximab, and azathioprine or mycophenolate use to an AE as determined by the investigator

End point title	Number of subjects where a relationship between Avacopan/Placebo, glucocorticoid use, cyclophosphamide, rituximab, and azathioprine or mycophenolate use to an AE as determined by the investigator

End point description:

AE=Adverse Event

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 421/week 60)

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Subjects				
Relationship of avacopan/placebo to an AE	103	100		
Relationship of glucocorticoid use to an AE	131	107		
Relationship of cyclophosphamide IV use to an AE	30	31		
Relationship of oral cyclophosphamide use to an AE	4	8		
Relationship of rituximab use to an AE	61	50		
Relationship of azathioprine use to an AE	35	28		
Relationship of mycophenolate use to an AE	9	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Certain safety endpoints of interest: infections, hepatic system abnormalities, WBC count decreases, and hypersensitivity.

End point title	Certain safety endpoints of interest: infections, hepatic system abnormalities, WBC count decreases, and hypersensitivity.

End point description:

WBC=White Blood Cell;
TEAE=Treatment-Emergent Adverse Event
TE = Treatment-Emergent

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 421/week 60)

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Subjects				
Any Treatment-Emergent Infection	124	113		
Any Serious Treatment-Emergent Infection	25	22		
Any Severe Treatment-Emergent Infection	10	12		
Any Treatment-Emergent Life-threatening Infection	2	1		
Any Treatment-Emergent Infection Leading to Death	2	1		
Any TEAE Associated with Hepatic Abnormalities	19	22		
Any TEAE Associated with Low WBC Counts	39	31		
Any TEAE Associated with hypersensitivity	70	68		
Any TE Infection Leading to Study Withdrawal	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline and shifts from baseline in all safety laboratory parameters - hematology

End point title	Change from baseline and shifts from baseline in all safety laboratory parameters - hematology

End point description:

Units differ for categories as follows:
Leukocytes/Neutrophils/Lymphocytes - 10^3 cells/µL
Eosinophils/Basophils/Monocytes/Platelets - 10^9 cells/L
Erythrocytes - 10^12 cells/L
Hemoglobin - g/dL
Hematocrit - percentage of red blood cells

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[21]	147[22]		
Units: Specified in end point description				
arithmetic mean (standard error)				
Leukocytes (Week 26)	-5.69 (± 0.338)	-5.94 (± 0.387)		
Leukocytes (Week 52)	-5.54 (± 0.365)	-5.62 (± 0.395)		
Neutrophils (Week 26)	-5.10 (± 0.338)	-5.24 (± 0.380)		
Neutrophils (Week 52)	-4.89 (± 0.361)	-4.95 (± 0.372)		
Lymphocytes (Week 26)	-0.62 (± 0.090)	-0.84 (± 0.099)		
Lymphocytes (Week 52)	-0.67 (± 0.090)	-0.82 (± 0.100)		
Eosinophils (Week 26)	0.07 (± 0.016)	0.07 (± 0.018)		
Eosinophils (Week 52)	0.05 (± 0.013)	0.07 (± 0.019)		
Basophils (Week 26)	-0.01 (± 0.004)	-0.00 (± 0.004)		
Basophils (Week 52)	-0.01 (± 0.004)	-0.01 (± 0.004)		
Monocytes (Week 26)	0.01 (± 0.022)	-0.04 (± 0.024)		
Monocytes (Week 52)	0.01 (± 0.024)	-0.01 (± 0.026)		
Platelets (Week 26)	-73.9 (± 8.49)	-77.1 (± 9.30)		
Platelets (Week 52)	-75.5 (± 8.01)	-73.8 (± 9.31)		
Erythrocytes (Week 26)	0.226 (± 0.0450)	0.252 (± 0.0432)		
Erythrocytes (Week 52)	0.244 (± 0.0410)	0.279 (± 0.0432)		
Hemoglobin (Week 26)	1.07 (± 0.129)	1.10 (± 0.120)		
Hemoglobin (Week 52)	1.20 (± 0.126)	1.27 (± 0.125)		
Hematocrit (Week 26)	2.6 (± 0.38)	2.7 (± 0.38)		
Hematocrit (Week 52)	3.0 (± 0.37)	3.2 (± 0.38)		

Notes:

[21] - The number of subjects analysed varied from 147 to 152 amongst the subcategories

[22] - The number of subjects analysed varied from 143 to 147 amongst the subcategories specified

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline and shifts from baseline in all safety laboratory parameters - serum chemistry

End point title	Change from baseline and shifts from baseline in all safety laboratory parameters - serum chemistry

End point description:

Units differ for categories as follows:

Lactate Dehydrogenase/Alkaline Phosphatase/Creatine Kinase/ Alanine Aminotransferase/ Aspartate Aminotransferase - U/L
Creatinine/ Urea Nitrogen/ Protein/ Cholesterol/ LDL Cholesterol/ Bilirubin - mg/dL

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[23]	150[24]		
Units: Specified in the end point description				
arithmetic mean (standard error)				
Lactate Dehydrogenase (Week 26)	2.3 (± 5.68)	-6.1 (± 5.40)		
Lactate Dehydrogenase (Week 52)	-8.6 (± 5.33)	-10.7 (± 4.80)		
Alkaline Phosphatase (Week 26)	-0.6 (± 2.47)	-3.9 (± 2.84)		
Alkaline Phosphatase (Week 52)	0.8 (± 1.77)	-4.0 (± 2.34)		
Creatine Kinase (Week 26)	47.6 (± 5.27)	76.8 (± 10.34)		
Creatine Kinase (Week 52)	57.6 (± 5.67)	76.3 (± 9.68)		
Alanine Aminotransferase (Week 26)	-6.8 (± 1.77)	-6.1 (± 1.54)		
Alanine Aminotransferase (Week 52)	-8.2 (± 1.57)	-7.2 (± 1.46)		
Aspartate Aminotransferase (Week 26)	1.9 (± 0.98)	2.5 (± 0.72)		
Aspartate Aminotransferase (Week 52)	0.5 (± 0.85)	2.0 (± 0.69)		
Creatinine (Week 26)	-0.105 (± 0.0569)	-0.195 (± 0.0508)		
Creatinine (Week 52)	-0.200 (± 0.0416)	-0.244 (± 0.0627)		
Urea Nitrogen (Week 26)	-9.4 (± 1.16)	-11.0 (± 1.32)		
Urea Nitrogen (Week 52)	-7.8 (± 1.11)	-11.9 (± 1.32)		
Protein (Week 26)	50 (± 50)	220 (± 47)		
Protein (Week 52)	160 (± 48)	250 (± 41)		
Cholesterol (Week 26)	19.0 (± 4.27)	7.4 (± 3.99)		
Cholesterol (Week 52)	13.8 (± 4.28)	9.3 (± 4.05)		
LDL Cholesterol (Week 26)	22.7 (± 3.66)	12.0 (± 3.47)		
LDL Cholesterol (Week 52)	21.7 (± 3.48)	11.9 (± 3.41)		
Bilirubin (Week 26)	0.065 (± 0.0182)	0.078 (± 0.0250)		
Bilirubin (Week 52)	0.053 (± 0.0185)	0.057 (± 0.0201)		

Notes:

[23] - The number of subjects analysed varied from 146 to 154 amongst the subcategories

[24] - The number of subjects analysed varied from 141 to 162 amongst the subcategories

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in vital signs

End point title	Change from baseline in vital signs

End point description:

Units differ for categories as follows:

Systolic Blood Pressure/ Diastolic Blood Pressure - mmHg
Pulse Rate - beats/min
Temperature - degree Celsius
Weight - kilogram(s)
BMI - kilogram(s)/ square meter

End point type	Secondary

End point timeframe:

Baseline, Week 26 and 52

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154[25]	154[26]		
Units: Specified in the end point description				
arithmetic mean (standard error)				
Systolic Blood Pressure (Week 26)	-2.5 (± 1.70)	-2.6 (± 1.54)		
Systolic Blood Pressure (Week 52)	-2.4 (± 1.64)	-1.0 (± 1.60)		
Diastolic Blood Pressure (Week 26)	2.7 (± 0.98)	0.5 (± 0.92)		
Diastolic Blood Pressure (Week 52)	1.4 (± 1.01)	1.4 (± 1.00)		
Pulse Rate (Week 26)	2.2 (± 1.12)	0.9 (± 1.25)		
Pulse Rate (Week 52)	-1.3 (± 1.07)	-0.3 (± 1.21)		
Temperature (Week 26)	-0.03 (± 0.043)	-0.11 (± 0.046)		
Temperature (Week 52)	0.04 (± 0.044)	-0.11 (± 0.048)		
Weight (Week 26)	3.33 (± 0.397)	1.93 (± 0.369)		
Weight (Week 52)	3.27 (± 0.477)	2.59 (± 0.487)		
BMI (Week 26)	1.13 (± 0.135)	0.67 (± 0.132)		
BMI (Week 52)	1.12 (± 0.164)	0.94 (± 0.179)		

Notes:

[25] - The number of subjects analysed varied from 148 to 154 amongst the subcategories specified

[26] - The number of subjects analysed varied from 148 to 154 amongst the subcategories specified

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects experiencing a relapse after previously achieving BVAS=0 during the study

End point title	Number of subjects experiencing a relapse after previously achieving BVAS=0 during the study

End point description:

BVAS=Birmingham Vasculitis Activity Score;
A relapse was defined as occurrence of at least one major item in the BVAS, or three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive visits, after:
a. having achieved remission at Week 26 (BVAS=0 and no glucocorticoids for ANCA-associated vasculitis within 4 weeks) or
b. having achieved BVAS=0 at any time during the treatment period

The BVAS form is divided into 9 organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis. The clinician only scores features believed to be due to active vasculitis. Completion of the form provides a numerical score, which ranges from 0 (best health) to 63 (worst health).

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 421/week 60)

End point values	Prednisone group	Avacopan group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	158		
Units: Participants	33	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day 1 throughout the study period (day 421/week 60)

Adverse event reporting additional description:

An AE was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study drug through 56 days following the last dose administered during the randomized treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Avacopan group

Reporting group description:

Avacopan plus cyclophosphamide/azathioprine or rituximab plus prednisone-matching placebo. The safety population included all subjects who were randomized and had received at least one dose of study drug.

Reporting group title	Prednisone group

Reporting group description:

Avacopan-matching placebo plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone. The safety population included all subjects who were randomized and had received at least one dose of study drug.

Serious adverse events	Avacopan group	Prednisone group	
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 166 (42.17%)	74 / 164 (45.12%)	
number of deaths (all causes)	2	4	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of skin			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Granulomatosis with polyangiitis			
subjects affected / exposed	5 / 166 (3.01%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Microscopic polyangiitis			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Arteriovenous fistula operation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 166 (1.20%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hernia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	12 / 166 (7.23%)	20 / 164 (12.20%)	
occurrences causally related to treatment / all	0 / 12	1 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	2 / 166 (1.20%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antineutrophil cytoplasmic antibody increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 166 (0.60%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 166 (0.00%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal ulcer			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal ulceration			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatic symptom disorder			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 166 (1.20%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 166 (0.60%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Medical observation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural vomiting			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar vertebral fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 166 (1.20%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 166 (1.20%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 166 (0.60%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrioventricular block first degree			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Mononeuropathy multiplex			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 166 (0.60%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 166 (0.60%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow toxicity			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatous lymphadenitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Episcleritis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 166 (0.00%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Large intestine polyp			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Abdominal hernia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis gastrointestinal			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	2 / 166 (1.20%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 166 (1.81%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 166 (4.82%)	6 / 164 (3.66%)	
occurrences causally related to treatment / all	2 / 9	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 166 (1.81%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related infection			
subjects affected / exposed	2 / 166 (1.20%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 166 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptococcosis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 166 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 166 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Avacopan group	Prednisone group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 166 (98.80%)	161 / 164 (98.17%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 166 (18.07%)	29 / 164 (17.68%)	
occurrences (all)	36	31	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	35 / 166 (21.08%)	40 / 164 (24.39%)	
occurrences (all)	39	56	
Fatigue			
subjects affected / exposed	17 / 166 (10.24%)	15 / 164 (9.15%)	
occurrences (all)	19	15	
Pyrexia			
subjects affected / exposed	15 / 166 (9.04%)	19 / 164 (11.59%)	
occurrences (all)	18	25	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis	Additional description: Worsening of vasculitis is reported as the Preferred Term of "anti-neutrophil cytoplasmic antibody-positive vasculitis".		
subjects affected / exposed	26 / 166 (15.66%)	34 / 164 (20.73%)	
occurrences (all)	30	46	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 166 (15.66%)	26 / 164 (15.85%)	
occurrences (all)	31	29	

Epistaxis			
subjects affected / exposed	14 / 166 (8.43%)	21 / 164 (12.80%)	
occurrences (all)	21	30	
Dyspnoea			
subjects affected / exposed	8 / 166 (4.82%)	11 / 164 (6.71%)	
occurrences (all)	11	14	
Oropharyngeal pain			
subjects affected / exposed	6 / 166 (3.61%)	12 / 164 (7.32%)	
occurrences (all)	7	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 166 (7.83%)	25 / 164 (15.24%)	
occurrences (all)	13	27	
Investigations			
Weight increased			
subjects affected / exposed	1 / 166 (0.60%)	17 / 164 (10.37%)	
occurrences (all)	1	19	
Blood creatinine increased			
subjects affected / exposed	10 / 166 (6.02%)	8 / 164 (4.88%)	
occurrences (all)	10	10	
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 166 (20.48%)	23 / 164 (14.02%)	
occurrences (all)	43	30	
Dizziness			
subjects affected / exposed	11 / 166 (6.63%)	10 / 164 (6.10%)	
occurrences (all)	14	10	
Tremor			
subjects affected / exposed	2 / 166 (1.20%)	10 / 164 (6.10%)	
occurrences (all)	2	11	
Paraesthesia			
subjects affected / exposed	9 / 166 (5.42%)	7 / 164 (4.27%)	
occurrences (all)	10	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 166 (7.83%)	18 / 164 (10.98%)	
occurrences (all)	13	19	

Leukopenia			
subjects affected / exposed	12 / 166 (7.23%)	14 / 164 (8.54%)	
occurrences (all)	15	20	
Increased tendency to bruise			
subjects affected / exposed	7 / 166 (4.22%)	10 / 164 (6.10%)	
occurrences (all)	7	11	
Lymphopenia			
subjects affected / exposed	6 / 166 (3.61%)	18 / 164 (10.98%)	
occurrences (all)	7	27	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	39 / 166 (23.49%)	34 / 164 (20.73%)	
occurrences (all)	54	46	
Diarrhoea			
subjects affected / exposed	25 / 166 (15.06%)	24 / 164 (14.63%)	
occurrences (all)	33	31	
Vomiting			
subjects affected / exposed	25 / 166 (15.06%)	21 / 164 (12.80%)	
occurrences (all)	29	27	
Abdominal pain upper			
subjects affected / exposed	11 / 166 (6.63%)	10 / 164 (6.10%)	
occurrences (all)	12	13	
Constipation			
subjects affected / exposed	11 / 166 (6.63%)	11 / 164 (6.71%)	
occurrences (all)	11	11	
Dyspepsia			
subjects affected / exposed	5 / 166 (3.01%)	10 / 164 (6.10%)	
occurrences (all)	6	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 166 (11.45%)	13 / 164 (7.93%)	
occurrences (all)	26	17	
Pruritus			
subjects affected / exposed	10 / 166 (6.02%)	10 / 164 (6.10%)	
occurrences (all)	15	11	
Alopecia			

subjects affected / exposed	7 / 166 (4.22%)	12 / 164 (7.32%)	
occurrences (all)	7	12	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	3 / 166 (1.81%)	9 / 164 (5.49%)	
occurrences (all)	3	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 166 (18.67%)	36 / 164 (21.95%)	
occurrences (all)	42	48	
Muscle spasms			
subjects affected / exposed	18 / 166 (10.84%)	37 / 164 (22.56%)	
occurrences (all)	23	47	
Back pain			
subjects affected / exposed	16 / 166 (9.64%)	22 / 164 (13.41%)	
occurrences (all)	16	22	
Myalgia			
subjects affected / exposed	16 / 166 (9.64%)	22 / 164 (13.41%)	
occurrences (all)	17	25	
Pain in extremity			
subjects affected / exposed	13 / 166 (7.83%)	13 / 164 (7.93%)	
occurrences (all)	13	13	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 166 (15.06%)	30 / 164 (18.29%)	
occurrences (all)	38	46	
Upper respiratory tract infection			
subjects affected / exposed	24 / 166 (14.46%)	24 / 164 (14.63%)	
occurrences (all)	28	33	
Urinary tract infection			
subjects affected / exposed	12 / 166 (7.23%)	23 / 164 (14.02%)	
occurrences (all)	19	33	
Pneumonia			
subjects affected / exposed	11 / 166 (6.63%)	11 / 164 (6.71%)	
occurrences (all)	12	11	
Sinusitis			

subjects affected / exposed	10 / 166 (6.02%)	12 / 164 (7.32%)	
occurrences (all)	10	12	
Bronchitis			
subjects affected / exposed	5 / 166 (3.01%)	10 / 164 (6.10%)	
occurrences (all)	7	11	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	12 / 166 (7.23%)	20 / 164 (12.20%)	
occurrences (all)	13	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2017	Administrative and editorial changes were made throughout. Relevant sections were revised to: • Indicate some changes regarding eligibility assessment • Indicate that the modified Schwartz equation is used to calculate eGFR for adolescents • Clarify that subjects may receive oral glucocorticoids if required • Indicate that enteric coated mycophenolate sodium would be allowed if mycophenolate mofetil was not tolerated/not available for use • Indicate that atovaquone may also be used for prophylaxis against Pneumocystis jirovecii infections • Update to be consistent with the guidance in the IB regarding laboratory abnormalities • Add that oral cyclophosphamide doses would be rounded down to the nearest 25 mg (or 50 mg if not available) Multiple changes were made to comply with requests from Regulatory agencies and Ethics Committees globally: • Indicated stratification factors were used as factors for the minimization algorithm • Definitions added for "women of childbearing potential" and "postmenopausal" • Inclusion criteria #2 and #19 were revised • Added urine pregnancy tests at Weeks 20, 32, and 45 • Referred Investigators to the side effect profile of prednisone and to the prescribing information for prednisone • Added a benefit and risk assessment section • Serious infections were added to the list of SAEs/AEs leading to withdrawal • Statements were added to indicate that: - Subjects who relapsed might require additional immunosuppressive therapy, and subjects who had a Grade 3< AE possibly related to study medication needed to be suspended until the event has resolved - Dosing regimens of prednisone, cyclophosphamide, rituximab, azathioprine, and mycophenolate were in line with current SOC - Lab reports indicating abnormalities for all subjects would be provided to Investigators - Clarify early study termination - All substantial protocol amendments had to be approved by the Competent Authorities prior to implementation
15 June 2018	• Study center visits were increased to implement additional monitoring for potential hepatotoxicity, as recommended by the DMC. • Instruction provided for actions to be taken if a subject develops a Grade 3 or higher AE considered possibly related to study medication to allow additional monitoring for potential hepatotoxicity, as recommended by the DMC. • Clarified that a relapse does not comprise treatment failure prior to Week 26. • Included guidance to the Investigators that in addition to events needing to be clearly documented in the EDC, that all local and national vaccination recommendations should be followed. • Clinical evaluations updated to include AEs and potential risks identified by the DMC based on review of unblinded safety data.
06 December 2018	Amended to include an open-label extension study; however, the sponsor decided not to proceed with the open-label extension study.

18 January 2019	• Deleted “first morning” in First morning UACR, random void was acceptable and first morning void was not necessary. • The definition of ITT population and treatment failures were amended to align with definition in the Statistical Analysis Plan. • Added hematology for study weeks 23, 29, 35, 42, and 48 and that the blood samples were to be collected for shipment to the central laboratory. • Section 4.4 Removal of Subjects from Therapy of Assessment was updated to add language on pausing for Grade 2 neutropenia and also provided further details on transaminase elevations that were in the previously issued (June 2018) safety notification letter. • Section 7.2.4.6 Laboratory Abnormalities was updated to incorporate recommendations of the DMC and rules for pausing administration of blinded study drug. • Clinical Evaluation was updated based on DMC review of unblinded safety data from all completed and ongoing studies of avacopan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported