Clinical trial results:
A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled Study of Verinurad and Allopurinol in Patients with Chronic Kidney Disease and Hyperuricaemia (SAPPHIRE)

Summary

EudraCT number	2018-004079-11
Trial protocol	HU SK CZ ES IT RO
Global end of trial date	17 December 2021

Results information

Result version number	v1
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	D5495C00002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151-85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com

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	17 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2021
Global end of trial reached?	Yes
Global end of trial date	17 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on urinary albumin to creatinine ratio at 6 months.

Protection of trial subjects:

Overall, the study was designed to minimise the risks to participating patients by excluding patients at high risk of AEs and by applying appropriate safety monitoring of recruited study patients. The doses selected were carefully considered in light of the target patient population. The potential benefits of developing a new treatment for CKD with hyperuricaemia therefore outweighed the limited risks to the patients exposed to treatment with verinurad and allopurinol in this trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2019
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	Czechia: 28
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 107
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Slovakia: 38
Country: Number of subjects enrolled	South Africa: 111
Country: Number of subjects enrolled	Spain: 76
Country: Number of subjects enrolled	United States: 337
Country: Number of subjects enrolled	Israel: 79
Worldwide total number of subjects	861
EEA total number of subjects	298

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	352
From 65 to 84 years	496
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled if:
- serum uric acid was greated than or equal to 6 mg/dL and
- estimated glomerular filtration rate was greated than or equal to 25 mL/min/1.73 m2 and
- urinary albumin to creatinine ratio was greated than or equal to 30 mg/g and less than or equal to 5000 mg/g

Pre-assignment

Screening details:

The total column for participants started should read 861. However, the participants that crossed-over from Low Dose to Switch Dose have been counted as additional participants

Period 1

Period 1 title	Overall Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	High Dose

Arm description:

Verinurad 12 mg plus allopurinol 300 mg

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

Dosage and administration details:

Allopurinol 300 mg to be taken, one time a day

Investigational medicinal product name	Verinurad
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Verinurad 12 mg to be taken, one time a day

Arm title	Intermediate Dose

Arm description:

Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg)

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

Dosage and administration details:

Allopurinol 300 mg to be taken, one time a day

Investigational medicinal product name	Verinurad
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Verinurad 7.5 mg to be taken, one time a day

Arm title	Low Dose

Arm description:

Verinurad 3 mg plus allopurinol 300 mg. As per Protocol Version 5.0, participants from 3 mg dose were switched to 24 mg at Visit 9.

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

Dosage and administration details:

Allopurinol 300 mg to be taken, one time a day

Investigational medicinal product name	Verinurad
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Verinurad 3 mg to be taken, one time a day

Arm title	Allopurinol

Arm description:

Allopurinol alone (Allopurinol): 300 mg

Arm type	Active comparator
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Allopurinol 300 mg to be taken alone, one time a day

Arm title	Placebo

Arm description:

Placebo only

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching allopurinol to be taken one time a day

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matching verinurad to be taken one time a day

Number of subjects in period 1	High Dose	Intermediate Dose	Low Dose
Started	172	172	173
Completed	137	143	131
Not completed	35	29	42
Adverse event, serious fatal	14	8	14
Consent withdrawn by subject	10	9	18
Physician decision	1	-	-
Failure to meet randomization criteria	-	1	1
Adverse event, non-fatal	1	3	2
Site terminated by sponsor	2	1	2
See listings in the clinical study report	5	5	3
Non-compliance with study drug	2	1	2
Study terminated by sponsor	-	1	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Allopurinol	Placebo
Started	171	173
Completed	145	147
Not completed	26	26
Adverse event, serious fatal	10	11
Consent withdrawn by subject	11	9
Physician decision	-	-
Failure to meet randomization criteria	-	-
Adverse event, non-fatal	2	-
Site terminated by sponsor	-	2
See listings in the clinical study report	2	2
Non-compliance with study drug	-	-
Study terminated by sponsor	-	-
Lost to follow-up	1	2

Period 2

Period 2 title	Switch Dose PA5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Switch Dose PA5

Arm description:

As per Protocol Version 5.0, participants from 3 mg dose (ie, Low Dose group) were switched to 24 mg at Visit 9. Participants received Verinurad 24 mg and Allopurinol 300 mg.

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

Dosage and administration details:

Allopurinol 300 mg to be taken, one time a day

Investigational medicinal product name	Verinurad
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Verinurad 3 mg to be taken, one time a day, up to Visit 9 and then switching to verinurad 24 mg to be taken, one time a day

Number of subjects in period 2[1]	Switch Dose PA5
Started	37
Completed	34
Not completed	3
Adverse event, serious fatal	1
Consent withdrawn by subject	1
See listings in the clinical study report	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subgroup of the Low Dose group.

Baseline characteristics

Reporting groups	
Reporting group title	High Dose
Reporting group description:	
Verinurad 12 mg plus allopurinol 300 mg	
Reporting group title	Intermediate Dose
Reporting group description:	
Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg)	
Reporting group title	Low Dose
Reporting group description:	
Verinurad 3 mg plus allopurinol 300 mg. As per Protocol Version 5.0, participants from 3 mg dose were switched to 24 mg at Visit 9.	
Reporting group title	Allopurinol
Reporting group description:	
Allopurinol alone (Allopurinol): 300 mg	
Reporting group title	Placebo
Reporting group description:	
Placebo only	

Reporting group values	High Dose	Intermediate Dose	Low Dose
Number of subjects	172	172	173
Age Categorical			
Age at Screening			
Units: Participants			
>=65	100	100	107
<65	72	72	66
Age continuous			
Age at Screening			
Units: years			
arithmetic mean	65.3	64.9	65.3
standard deviation	± 10.0	± 11.2	± 11.2
Sex: Female, Male			
Units: Participants			
Female	69	53	57
Male	103	119	116
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	42	45	37
Not Hispanic or Latino	130	127	136
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
"Unknown or Not Reported" comprises CSR categories "Other" and "Missing". The below group "More than one race" was not an item on the case report form, so the numbers zero (0) reported below does not necessarily reflect the actual multiple-race status of the population.			
Units: Subjects			
American Indian or Alaska Native	4	4	8
Asian	4	3	5
Native Hawaiian or Other Pacific Islander	1	0	0

Black or African American	25	24	24
White	122	125	126
More than one race	0	0	0
Unknown or Not Reported	16	16	10
Region of Enrollment			
Country			
Units: Subjects			
Czech Republic	6	7	3
France	2	1	2
Hungary	22	25	19
Israel	15	17	19
Italy	0	2	0
Mexico	6	5	8
Poland	1	4	2
Romania	2	5	5
Slovakia	8	6	13
South Africa	23	21	20
Spain	17	12	14
United States	70	67	68
Age, Continuous			
Age at Screening			
Units: Years			
arithmetic mean	65.3	64.9	65.3
standard deviation	± 10.0	± 11.2	± 11.2

Reporting group values	Allopurinol	Placebo	Total
Number of subjects	171	173	861
Age Categorical			
Age at Screening			
Units: Participants			
>=65	95	107	509
<65	76	66	352
Age continuous			
Age at Screening			
Units: years			
arithmetic mean	65.1	65.8	
standard deviation	± 11.0	± 10.4	-
Sex: Female, Male Units: Participants			
Female	55	50	284
Male	116	123	577
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	40	41	205
Not Hispanic or Latino	131	132	656
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
"Unknown or Not Reported" comprises CSR categories "Other" and "Missing". The below group "More than one race" was not an item on the case report form, so the numbers zero (0) reported below does not necessarily reflect the actual multiple-race status of the population.			
Units: Subjects			
American Indian or Alaska Native	5	8	29

Asian	4	4	20
Native Hawaiian or Other Pacific Islander	1	0	2
Black or African American	23	20	116
White	118	131	622
More than one race	0	0	0
Unknown or Not Reported	20	10	72
Region of Enrollment			
Country			
Units: Subjects			
Czech Republic	7	5	28
France	0	2	7
Hungary	19	22	107
Israel	15	13	79
Italy	1	2	5
Mexico	7	10	36
Poland	3	5	15
Romania	3	7	22
Slovakia	5	6	38
South Africa	24	23	111
Spain	16	17	76
United States	71	61	337
Age, Continuous			
Age at Screening			
Units: Years			
arithmetic mean	65.1	65.8	
standard deviation	± 11.0	± 10.4	-

End points

End points reporting groups

Reporting group title	High Dose
Reporting group description:	
Verinurad 12 mg plus allopurinol 300 mg	
Reporting group title	Intermediate Dose
Reporting group description:	
Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg)	
Reporting group title	Low Dose
Reporting group description:	
Verinurad 3 mg plus allopurinol 300 mg. As per Protocol Version 5.0, participants from 3 mg dose were switched to 24 mg at Visit 9.	
Reporting group title	Allopurinol
Reporting group description:	
Allopurinol alone (Allopurinol): 300 mg	
Reporting group title	Placebo
Reporting group description:	
Placebo only	
Reporting group title	Switch Dose PA5
Reporting group description:	
As per Protocol Version 5.0, participants from 3 mg dose (ie, Low Dose group) were switched to 24 mg at Visit 9. Participants received Verinurad 24 mg and Allopurinol 300 mg.	
Subject analysis set title	High Dose versus Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
High dose (verinurad 12 mg plus allopurinol 300 mg) versus placebo for uACR	
Subject analysis set title	High Dose and Intermediate Dose combined versus Allopurinol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
High dose (verinurad 12 mg plus allopurinol 300 mg) and intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg) combined versus allopurinol (allopurinol 300 mg) for uACR	
Subject analysis set title	Intermediate Dose versus Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg) versus placebo for uACR, sUA, eGFR, and S-creatinine (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)	
Subject analysis set title	Low Dose versus Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Low dose (verinurad 3 mg plus allopurinol 300 mg) versus placebo for uACR	
Subject analysis set title	High Dose versus Allopurinol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
High dose (verinurad 12 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300 mg) for uACR	
Subject analysis set title	Intermediate Dose versus Allopurinol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300 mg) for uACR	
Subject analysis set title	Low Dose versus Allopurinol

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Low dose (verinurad 3 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300mg) for uACR

Subject analysis set title	Allopurinol versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Allopurinol (allopurinol 300mg) versus placebo for uACR and P-cystatin C (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Switch dose PA5 vs PA5-Switcher Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Switch dose PA5 (verinurad 3 mg plus allopurinol 300 mg up to V9 then verinurad 24 mg plus allopurinol 300 mg) versus PA5-Switcher Placebo for uACR

Subject analysis set title	High Dose versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

High dose (verinurad 12 mg plus allopurinol 300 mg) versus placebo for sUA, eGFR, and S-creatinine (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Low Dose versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Low dose (verinurad 3 mg plus allopurinol 300 mg) versus placebo for sUA, eGFR, and S-creatinine (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	High Dose versus Allopurinol
Subject analysis set type	Sub-group analysis

Subject analysis set description:

High dose (verinurad 12 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300 mg) for sUA, eGFR, and S-creatinine (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Intermdiate Dose versus Allopurinol
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300 mg) for sUA, eGFR, S-creatinine, and P-cystatin C (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Low Dose versus Allopurinol
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Low dose (verinurad 3 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300mg) for sUA, eGFR, and S-creatinine (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Allopurinol versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Allopurinol (allopurinol 300mg) versus placebo for sUA, eGFR, and S-creatinine (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Switch dose PA5 vs PA5-Switcher Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Switch dose PA5 (verinurad 3 mg plus allopurinol 300 mg up to V9 then verinurad 24 mg plus allopurinol 300 mg) versus PA5-Switcher Placebo for sUA

Subject analysis set title	Verinurad 0 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Verinurad 0 mg plus allopurinol 300mg for uACR

Subject analysis set title	Verinurad 3 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Verinurad 3 mg plus allopurinol 300mg for uACR and sUA (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Verinurad 7.5 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Verinurad 7.5 mg plus allopurinol 300mg for uACR

Subject analysis set title	Verinurad 12 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Verinurad 12 mg plus allopurinol 300mg for uACR and sUA (the numbers of subjects in each analysis are not necessarily the same subjects, just the same number of subjects is shared between these analyses)

Subject analysis set title	Verinurad 0 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Verinurad 0 mg plus allopurinol 300mg for sUA

Subject analysis set title	Verinurad 7.5 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Verinurad 7.5 mg plus allopurinol 300mg for sUA

Subject analysis set title	High Dose versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

High dose (verinurad 12 mg plus allopurinol 300 mg) versus placebo for P-cystatin C

Subject analysis set title	Intermediate Dose versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Intermediate dose (verinurad 7.5 mg plus allopurinol 300 mg) versus placebo for P-cystatin C

Subject analysis set title	Low Dose versus Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Low dose (verinurad 3 mg plus allopurinol 300 mg) versus placebo for P-cystatin C

Subject analysis set title	High Dose versus Allopurinol
Subject analysis set type	Sub-group analysis

Subject analysis set description:

High dose (verinurad 12 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300 mg) for P-cystatin C

Subject analysis set title	Low Dose versus Allopurinol
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Low dose (verinurad 3 mg plus allopurinol 300 mg) versus allopurinol (allopurinol 300mg) for P-cystatin C

Primary: Urinary albumin to creatinine ratio (uACR) (mg/g) change from baseline at 6 months (Visit 8), repeated measures mixed model (MMRM)

End point title	Urinary albumin to creatinine ratio (uACR) (mg/g) change from baseline at 6 months (Visit 8), repeated measures mixed model (MMRM)[1]

End point description:

Analyses of change from baseline in uACR at 6 months (Visit 8) focused on:

-High dose vs Placebo**
-High dose and Inter. dose combined vs Allopurinol alone**
-Inter. dose vs Placebo
-Low dose vs Placebo
-High dose vs Allopurinol
-Inter. dose vs Allopurinol
-Low dose vs Allopurinol
-Allopurinol vs Placebo**
**indicates where tests of no treatment difference were controlled for multiplicity (a hierarchical testing procedure).
The hierarchical testing procedure ensured the familywise error rate in the strong sense is controlled at a level of 0.1 (10%). The first test of change from baseline in uACR for High dose vs Placebo reached statistical significance, p=0.0648. The second test of High dose and Inter. dose vs Allopurinol did not, p=0.6296. Consequently, Allopurinol vs Placebo was not statistically significant even if the p-value is below 0.1, p=0.0263. For High dose and Inter. dose combined the 2 categories merged forming 1 new temporary category. Geometric mean ratio is presented.

End point type	Primary

End point timeframe:

Baseline to 9 months (Visit 9); analysis at 6 months (Visit 8)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A statistical analysis did occur for this analysis, the results are presented in this section, we have geometric mean ratios, confidence intervals and relevant P-values. Please see this in this section.

End point values	High Dose versus Placebo	High Dose and Intermediate Dose combined versus Allopurinol	Intermediate Dose versus Placebo	Low Dose versus Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	284	434	297	290
Units: mg/g				
geometric mean (confidence interval 95%)	0.8300 (0.6810 to 1.012)	1.043 (0.8793 to 1.237)	0.8369 (0.6887 to 1.017)	0.8499 (0.6984 to 1.034)

End point values	High Dose versus Allopurinol	Intermediate Dose versus Allopurinol	Low Dose versus Allopurinol	Allopurinol versus Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	283	296	289	291
Units: mg/g				
geometric mean (confidence interval 95%)	1.037 (0.8506 to 1.265)	1.046 (0.8603 to 1.272)	1.062 (0.8725 to 1.293)	0.8001 (0.6573 to 0.9739)

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary albumin to creatinine ratio (uACR) (mg/g) change from baseline at 12 months (Visit 10), repeated measures mixed model (MMRM)

End point title	Urinary albumin to creatinine ratio (uACR) (mg/g) change from baseline at 12 months (Visit 10), repeated measures mixed

	model (MMRM)

End point description:

Change from baseline in uACR at 12 months (Visit 10) for comparison of Switch dose protocol version 5.0 (PA5) versus Placebo.

The statistical model applied was an MMRM, which was basically the same as the one applied in the primary analysis but adjusted for a 12 month horizon and adapted to the double-capsule regimen from Visit 9 on.

The geometric mean ratio is presented.

End point type	Secondary

End point timeframe:

Baseline to 12 months (Visit 10); analysis at 12 months (Visit 10)

End point values	Switch dose PA5 vs PA5-Switcher Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	78			
Units: mg/g				
geometric mean (confidence interval 95%)	1.016 (0.7437 to 1.388)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum uric acid (sUA) (mg/dL) change from baseline at 6 months (Visit 8), repeated measures mixed model (MMRM)

End point title	Serum uric acid (sUA) (mg/dL) change from baseline at 6 months (Visit 8), repeated measures mixed model (MMRM)

End point description:

Change from baseline in sUA at 6 months (Visit 8), there were 7 comparisons requested for each endpoint, namely:

- High dose vs Placebo
- Inter. dose vs Placebo
- Low dose vs Placebo
- High dose vs Allopurinol
- Inter. dose vs Allopurinol
- Low dose vs Allopurinol
- Allopurinol vs Placebo.

The geometric mean ratio is presented.

End point type	Secondary

End point timeframe:

Baseline to 9 months (Visit 9); analysis at 6 months (Visit 8)

End point values	Intermediate Dose versus Placebo	High Dose versus Placebo	Low Dose versus Placebo	High Dose versus Allopurinol
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	297	285	291	280
Units: mg/dL				
geometric mean (confidence interval 95%)	0.5810 (0.5362 to 0.6295)	0.5098 (0.4701 to 0.5528)	0.6096 (0.5623 to 0.6609)	0.8184 (0.7544 to 0.8878)

End point values	Intermdiate Dose versus Allopurinol	Low Dose versus Allopurinol	Allopurinol versus Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	292	286	289	
Units: mg/dL				
geometric mean (confidence interval 95%)	0.9327 (0.8604 to 1.011)	0.9786 (0.9024 to 1.061)	0.6229 (0.5744 to 0.6755)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum uric acid (sUA) change from baseline at 12 months (Visit 10), repeated measures mixed model (MMRM)

End point title	Serum uric acid (sUA) change from baseline at 12 months (Visit 10), repeated measures mixed model (MMRM)

End point description:

Change from baseline in sUA at 12 months (Visit 10) for comparison of Switch dose protocol version 5.0 (PA5) versus Placebo.

The geometric mean ratio is presented.

End point type	Secondary

End point timeframe:

Baseline to 12 months (Visit 10); analysis at 12 months (Visit 10)

End point values	Switch dose PA5 vs PA5-Switcher Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	74			
Units: Geometric Mean Ratio				
geometric mean (confidence interval 95%)	0.5540 (0.4825 to 0.6362)			

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary albumin to creatinine ratio (uACR) dose-response at 6 months (Visit 8)

End point title	Urinary albumin to creatinine ratio (uACR) dose-response at 6 months (Visit 8)

End point description:

The change from baseline in uACR at 6 months (Visit 8) was observed to graphically assess the dose-response relationship among 3 doses of verinurad and allopurinol. No obvious relationship between uACR reduction at 6 months and verinurad dose was observed.

End point type	Secondary

End point timeframe:

Change from baseline to 6 months (Visit 8)

End point values	Verinurad 0 mg	Verinurad 3 mg	Verinurad 7.5 mg	Verinurad 12 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[2]	144[3]	151[4]	138[5]
Units: Number of participants	0	0	0	0

Notes:

[2] - In the CSR the results are presented graphically.

0000 = not applicable

[3] - In the CSR the results are presented graphically.

0000 = not applicable

[4] - In the CSR the results are presented graphically.

0000 = not applicable

[5] - In the CSR the results are presented graphically.

0000 = not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) change from baseline at 6 months (V8), repeated measures mixed model (MMRM)

End point title	Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) change from baseline at 6 months (V8), repeated measures mixed model (MMRM)

End point description:

Change from baseline in eGFR at 6 months (Visit 8), there were 7 comparisons requested for this endpoint, namely:

- High dose vs Placebo
- Inter. dose vs Placebo
- Low dose vs Placebo
- High dose vs Allopurinol
- Inter. dose vs Allopurinol
- Low dose vs Allopurinol
- Allopurinol vs Placebo.

The geometric mean ratio is presented.

End point type	Secondary

End point timeframe:

Baseline to 9 months (Visit 9); analysis at 6 months (Visit 8)

End point values	Intermediate Dose versus Placebo	High Dose versus Placebo	Low Dose versus Placebo	High Dose versus Allopurinol
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	297	285	291	280
Units: mL/min/1.73 m²				
geometric mean (confidence interval 95%)	0.9730 (0.9307 to 1.017)	1.009 (0.9647 to 1.056)	1.010 (0.9660 to 1.056)	1.023 (0.9773 to 1.070)

End point values	Intermdiate Dose versus Allopurinol	Low Dose versus Allopurinol	Allopurinol versus Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	292	286	289	
Units: mL/min/1.73 m²				
geometric mean (confidence interval 95%)	0.9859 (0.9429 to 1.031)	1.024 (0.9786 to 1.071)	0.9868 (0.9436 to 1.032)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum uric acid (sUA) dose-response at 6 months (Visit 8)

End point title	Serum uric acid (sUA) dose-response at 6 months (Visit 8)

End point description:

The change from baseline in sUA at 6 months (Visit 8) was observed to assess the dose-response relationship among 3 doses of verinurad and allopurinol and placebo. No relationship between sUA reduction at 6 months and verinurad dose was observed.

End point type	Secondary

End point timeframe:

Change from baseline to 6 months (Visit 8)

End point values	Verinurad 3 mg	Verinurad 12 mg	Verinurad 0 mg	Verinurad 7.5 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	144[6]	138[7]	142[8]	150[9]
Units: Number of participants	0	0	0	0

Notes:

[6] - In the CSR the results are presented graphically.

0000 = not applicable
[7] - In the CSR the results are presented graphically.

0000 = not applicable
[8] - In the CSR the results are presented graphically.

0000 = not applicable
[9] - In the CSR the results are presented graphically.

0000 = not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) change from baseline at 12 months (Visit 10)

End point title	Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²) change from baseline at 12 months (Visit 10)

End point description:

Change from baseline in eGFR at 12 months (Visit 10) for the following treatments:

- High Dose
- Inter. Dose
- Low Dose (a)
- Switch Dose protocol version 5.0 (PA5) (b)
- Allopurinol
- Placebo

(a) Subjects that switched from Verinurad 3 mg to Verinurad 24 mg at Visit 9 are not included in this group for Visit 10.
(b) Contains all subjects randomized to the low dose group that later switched to Verinurad 24 mg plus Allopurinol 300 mg.

This endpoint was analysed with descriptive statistics.

End point type	Secondary

End point timeframe:

Change from baseline to 12 months (Visit 10)

End point values	High Dose	Switch Dose PA5	Intermediate Dose	Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	34	137	99
Units: mL/min/1.73 m²				
geometric mean (geometric coefficient of variation)	0.9809 (± 20.09)	1.101 (± 27.23)	0.9454 (± 21.24)	0.9613 (± 17.59)

End point values	Allopurinol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	138		
Units: mL/min/1.73 m²				
geometric mean (geometric coefficient of variation)	0.9593 (± 23.36)	0.9469 (± 23.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: S-creatinine (mg/dL) change from baseline at 6 months (V8), repeated measures mixed model (MMRM)

End point title	S-creatinine (mg/dL) change from baseline at 6 months (V8), repeated measures mixed model (MMRM)

End point description:

Change from baseline in S-creatinine at 6 months (Visit 8), there were 7 comparisons requested for this endpoint, namely:

- High dose vs Placebo
- Inter. dose vs Placebo
- Low dose vs Placebo
- High dose vs Allopurinol
- Inter. dose vs Allopurinol
- Low dose vs Allopurinol
- Allopurinol vs Placebo.

The geometric mean ratio is presented.

End point type	Secondary

End point timeframe:

Baseline to 9 months (Visit 9); analysis at 6 months (Visit 8)

End point values	Intermediate Dose versus Placebo	High Dose versus Placebo	Low Dose versus Placebo	High Dose versus Allopurinol
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	297	285	291	280
Units: Geometric Mean Ratio				
geometric mean (confidence interval 95%)	1.023 (0.9857 to 1.062)	0.9888 (0.9523 to 1.027)	0.9901 (0.9538 to 1.028)	0.9801 (0.9437 to 1.018)

End point values	Intermdiate Dose versus Allopurinol	Low Dose versus Allopurinol	Allopurinol versus Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	292	286	289	
Units: Geometric Mean Ratio				
geometric mean (confidence interval 95%)	1.014 (0.9770 to 1.053)	0.9814 (0.9452 to 1.019)	1.009 (0.9718 to 1.047)	

Statistical analyses

No statistical analyses for this end point

Secondary: S-creatinine (mg/dL) change from baseline at 12 months (Visit 10)

End point title	S-creatinine (mg/dL) change from baseline at 12 months (Visit 10)

End point description:

Change from baseline in S-creatinine at 12 months (Visit 10) for the following treatments:

- High Dose
- Inter. Dose
- Low Dose (a)
- Switch Dose protocol version 5.0 (PA5) (b)
- Allopurinol
- Placebo

(a) Subjects that switched from Verinurad 3 mg to Verinurad 24 mg at Visit 9 are not included in this group for Visit 10.
(b) Contains all subjects randomized to the low dose group that later switched to Verinurad 24 mg plus Allopurinol 300 mg.

This endpoint was analysed with descriptive statistics.

End point type	Secondary

End point timeframe:

Change from baseline to 12 months (Visit 10)

End point values	High Dose	Switch Dose PA5	Intermediate Dose	Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	34	137	99
Units: mg/dL				
geometric mean (geometric coefficient of variation)	1.011 (± 18.57)	0.9078 (± 17.66)	1.038 (± 18.37)	1.026 (± 17.15)

End point values	Allopurinol	Placebo		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	138		
Units: mg/dL				
geometric mean (geometric coefficient of variation)	1.028 (± 24.44)	1.043 (± 20.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: P-cystatin C (mg/L) change from baseline at 6 months (V8), repeated measures mixed model (MMRM)

End point title	P-cystatin C (mg/L) change from baseline at 6 months (V8), repeated measures mixed model (MMRM)

End point description:

Change from baseline in P-cystatin C at 6 months (Visit 8), there were 7 comparisons requested for this endpoint, namely:

- High dose vs Placebo
- Inter. dose vs Placebo
- Low dose vs Placebo
- High dose vs Allopurinol
- Inter. dose vs Allopurinol
- Low dose vs Allopurinol
- Allopurinol vs Placebo.

The geometric mean ratio is presented.

End point type	Secondary

End point timeframe:

Baseline to 9 months (Visit 9); analysis at 6 months (Visit 8)

End point values	Allopurinol versus Placebo	Intermdiate Dose versus Allopurinol	High Dose versus Placebo	Intermediate Dose versus Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	291	292	288	299
Units: Geometric Mean Ratio				
geometric mean (confidence interval 95%)	1.024 (0.9908 to 1.058)	1.014 (0.9813 to 1.048)	1.009 (0.9758 to 1.042)	1.038 (1.005 to 1.073)

End point values	Low Dose versus Placebo	High Dose versus Allopurinol	Low Dose versus Allopurinol	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	294	281	287	
Units: Geometric Mean Ratio				
geometric mean (confidence interval 95%)	1.018 (0.9856 to 1.052)	0.9849 (0.9528 to 1.018)	0.9946 (0.9623 to 1.028)	

Statistical analyses

No statistical analyses for this end point

Secondary: P-cystatin C (mg/L) change from baseline at 12 months (Visit 10)

End point title	P-cystatin C (mg/L) change from baseline at 12 months (Visit 10)

End point description:

Change from baseline in S-creatinine at 12 months (Visit 10) for the following treatments:

- High Dose
- Inter. Dose
- Low Dose (a)
- Switch Dose protocol version 5.0 (PA5) (b)
- Allopurinol
- Placebo

(a) Subjects that switched from Verinurad 3 mg to Verinurad 24 mg at Visit 9 are not included in this group for Visit 10.
(b) Contains all subjects randomized to the low dose group that later switched to Verinurad 24 mg plus Allopurinol 300 mg.

This endpoint was analysed with descriptive statistics.

End point type	Secondary

End point timeframe:

Change from baseline to 12 months (Visit 10)

End point values	High Dose	Switch Dose PA5	Intermediate Dose	Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	34	141	99
Units: mg/L				
geometric mean (geometric coefficient of variation)	1.070 (± 17.98)	1.018 (± 13.68)	1.079 (± 15.63)	1.065 (± 16.51)

End point values	Allopurinol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	138		
Units: mg/L				
geometric mean (geometric coefficient of variation)	1.083 (± 23.13)	1.048 (± 14.89)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events with an onset date on or after date of visit 3 until the day of last attended scheduled visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Inter.Dose
Reporting group description: -	
Reporting group title	High Dose
Reporting group description: -	
Reporting group title	Low Dose

Reporting group description:

Adverse events reported under the Low Dose group occurred "while on 3 mg verinurad", whereas the adverse events reported under Switch Dose PA5 group occurred after switching to 24 mg verinuad (while on 24 mg)

Reporting group title	Switch Dose PA5
Reporting group description: -	
Reporting group title	Allopurinol
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Inter.Dose	High Dose	Low Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 172 (22.67%)	36 / 172 (20.93%)	40 / 172 (23.26%)
number of deaths (all causes)	8	14	13
number of deaths resulting from adverse events	8	14	13
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial carcinoma			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Colon cancer			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Lung neoplasm			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to liver			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to the mediastinum			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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 disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Aortic stenosis			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Shock			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Superficial vein thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
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			
Cardiac death			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Chest pain			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 172 (0.00%)	3 / 172 (1.74%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 2
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Oedema peripheral			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Sudden death			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcoidosis			

subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermenstrual bleeding			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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 respiratory failure			
subjects affected / exposed	0 / 172 (0.00%)	2 / 172 (1.16%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	2 / 172 (1.16%)	0 / 172 (0.00%)	0 / 172 (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
Epistaxis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Delirium			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test positive			

subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns second degree			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Femur fracture			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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 disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina pectoris			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Atrial fibrillation			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
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 arrest			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 172 (1.16%)	2 / 172 (1.16%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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 failure congestive			
subjects affected / exposed	1 / 172 (0.58%)	1 / 172 (0.58%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Coronary artery stenosis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Myocardial infarction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paroxysmal atrioventricular block			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
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			
Bell's palsy			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Carotid artery occlusion			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Cerebral arteriosclerosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 172 (0.58%)	2 / 172 (1.16%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epilepsy			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Hypoxic-ischaemic encephalopathy			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Migraine			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Peroneal nerve palsy			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Transient ischaemic attack			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 172 (0.58%)	2 / 172 (1.16%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			

subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Cataract			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Rhegmatogenous retinal detachment			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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

Diarrhoea			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Duodenal ulcer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
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 acute			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
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 obstruction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Cholelithiasis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic epidermal necrolysis			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 172 (0.00%)	3 / 172 (1.74%)	3 / 172 (1.74%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Nephropathy			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Renal failure			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Flank pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Osteoarthritis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Psoriatic arthropathy			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Atypical pneumonia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Bacterial sepsis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Cellulitis			
subjects affected / exposed	1 / 172 (0.58%)	1 / 172 (0.58%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complicated appendicitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Diabetic foot infection			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 172 (2.33%)	3 / 172 (1.74%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia bacterial			

subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 172 (0.58%)	1 / 172 (0.58%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 172 (1.16%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 172 (1.16%)	1 / 172 (0.58%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	3 / 172 (1.74%)	3 / 172 (1.74%)	4 / 172 (2.33%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 2
COVID-19 pneumonia			
subjects affected / exposed	3 / 172 (1.74%)	4 / 172 (2.33%)	5 / 172 (2.91%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 3
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 172 (0.58%)	0 / 172 (0.00%)	0 / 172 (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
Diabetic ketoacidosis			

subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
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			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Hypoglycaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Hyponatraemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Metabolic acidosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 172 (0.58%)	0 / 172 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 172 (0.00%)	0 / 172 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Switch Dose PA5	Allopurinol	Placebo
Total subjects affected by serious			

adverse events			
subjects affected / exposed	4 / 37 (10.81%)	42 / 171 (24.56%)	35 / 173 (20.23%)
number of deaths (all causes)	1	10	11
number of deaths resulting from adverse events	1	10	11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to the mediastinum			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Neuroendocrine tumour			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Prostate cancer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	2 / 173 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Peripheral artery occlusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial vein thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chest pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Vascular stent thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Sarcoidosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Intermenstrual bleeding			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Asthma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			

subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Mental status changes			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 37 (0.00%)	2 / 171 (1.17%)	0 / 173 (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
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns second degree			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture displacement			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
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 myocardial infarction			
subjects affected / exposed	1 / 37 (2.70%)	2 / 171 (1.17%)	2 / 173 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 37 (0.00%)	2 / 171 (1.17%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 37 (0.00%)	2 / 171 (1.17%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 37 (2.70%)	1 / 171 (0.58%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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 arrest			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Cardiac failure			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	3 / 173 (1.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 37 (0.00%)	4 / 171 (2.34%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paroxysmal atrioventricular block			

subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Right ventricular failure			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Bell's palsy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery occlusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral arteriosclerosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 37 (2.70%)	1 / 171 (0.58%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Embolic stroke			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Ischaemic stroke			
subjects affected / exposed	1 / 37 (2.70%)	2 / 171 (1.17%)	2 / 173 (1.16%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
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 loss anaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Vertigo			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal detachment			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhegmatogenous retinal detachment			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	0 / 171 (0.00%)	0 / 173 (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
Melaena			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
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 acute			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Rash			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Nephropathy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Urinary tract obstruction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Flank pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
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			
Abscess limb			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	2 / 173 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complicated appendicitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Erysipelas			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
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			

subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Localised infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	2 / 171 (1.17%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	0 / 37 (0.00%)	6 / 171 (3.51%)	4 / 173 (2.31%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	3 / 171 (1.75%)	3 / 173 (1.73%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 171 (0.58%)	0 / 173 (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
Hypoglycaemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 171 (1.17%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 37 (0.00%)	0 / 171 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Inter.Dose	High Dose	Low Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 172 (18.60%)	32 / 172 (18.60%)	28 / 172 (16.28%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 172 (2.91%)	0 / 172 (0.00%)	2 / 172 (1.16%)
occurrences (all)	5	0	2
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 172 (5.23%)	6 / 172 (3.49%)	5 / 172 (2.91%)
occurrences (all)	12	6	7
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 172 (2.33%)	8 / 172 (4.65%)	6 / 172 (3.49%)
occurrences (all)	4	9	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 172 (2.91%)	7 / 172 (4.07%)	2 / 172 (1.16%)
occurrences (all)	5	7	2
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	5 / 172 (2.91%)	9 / 172 (5.23%)	4 / 172 (2.33%)
occurrences (all)	6	10	4
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	6 / 172 (3.49%)	3 / 172 (1.74%)	9 / 172 (5.23%)
occurrences (all)	7	3	9
Hyperkalaemia			
subjects affected / exposed	4 / 172 (2.33%)	5 / 172 (2.91%)	3 / 172 (1.74%)
occurrences (all)	4	5	3

Non-serious adverse events	Switch Dose PA5	Allopurinol	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)	39 / 171 (22.81%)	49 / 173 (28.32%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 37 (0.00%)	9 / 171 (5.26%)	2 / 173 (1.16%)
occurrences (all)	0	10	8
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 37 (0.00%)	12 / 171 (7.02%)	7 / 173 (4.05%)
occurrences (all)	0	13	8
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 37 (0.00%)	3 / 171 (1.75%)	11 / 173 (6.36%)
occurrences (all)	0	4	13
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	8 / 171 (4.68%)	11 / 173 (6.36%)
occurrences (all)	1	9	12
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 37 (2.70%)	5 / 171 (2.92%)	11 / 173 (6.36%)
occurrences (all)	1	6	11
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 37 (0.00%)	5 / 171 (2.92%)	13 / 173 (7.51%)
occurrences (all)	0	7	19

Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	5 / 171 (2.92%) 5	10 / 173 (5.78%) 13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2019	Reduction of sample size, specification of the allopurinol formulation was changed and clarifications for procedures were added.
23 April 2020	Addition of exclusion criteria, pregnancy tests, gout flare endpoints, guidelines for temporary interruption of study treatments, and guidelines related to COVID-19 pandemic.
06 August 2020	Updated allele testing was made mandatory for all patients prior to randomisation and limited up-titration steps in patients with low estimated glomerular filtration rate were added.
18 November 2020	Most changes were implemented to allow 24 mg verinurad to be assessed in the study to fully explore the verinurad dose range, and to shorten the study treatment to 60 weeks in all patients due to shortage of investigational product.

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.

The study was initially planned to be 108 weeks. However, following the amendment in Protocol Version 5.0, all patients discontinued therapy after 60 weeks (Visit 10). Subjects that were on Low dose at Visit 9 were switched to 24 mg dose.

Notes: