Clinical trial results:
A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Nemolizumab in Subjects with Chronic Kidney Disease with Associated Severe Pruritus

Summary

EudraCT number	2021-004766-35
Trial protocol	ES HU PL
Global end of trial date	04 January 2024

Results information

Result version number	v1 (current)
This version publication date	29 January 2025
First version publication date	29 January 2025

Trial information

Trial identification

Sponsor protocol code	RD.06.SPR.204358 (NIKAIA 1)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05075408
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 117122

Notes:

Sponsors

Sponsor organisation name	Galderma S.A.
Sponsor organisation address	Zählerweg 10, Zug, Switzerland, 6300
Public contact	Clinical Trial Information Desk, Galderma S.A., CTA.Coordinator@galderma.com
Scientific contact	Clinical Trial Information Desk, Galderma S.A., CTA.Coordinator@galderma.com
Sponsor organisation name	Galderma Research & Development, LLC
Sponsor organisation address	2001 Ross Avenue, Suite 1600, Dallas, United States, TX 75201
Public contact	Clinical Trial Information Desk, Galderma S.A., CTA.Coordinator@galderma.com
Scientific contact	Clinical Trial Information Desk, Galderma S.A., CTA.Coordinator@galderma.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	04 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of nemolizumab compared with placebo in reducing the intensity of pruritus after a 12-week treatment period in adult hemodialysis subjects with moderate-to-severe pruritus.

Protection of trial subjects:

The study was conducted in accordance with the accepted version of the Declaration of Helsinki, in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted. The protocol, the informed consent form (ICF), other written material given to the subjects, and any other relevant study documentation after the document and their amendments were reviewed and approved by a duly constituted IEC or IRB before implementation. For each subject, written informed consent was obtained before any protocol-related activities.

Background therapy:

The following 2 categories were to be considered for prior and concomitant therapies: 1) Drugs/therapies included, but were not limited to, prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations and 2) Medical and surgical procedures (e.g., phototherapy, exodontia) whose sole purpose was diagnosis (non-therapeutic) were not included.
Unless specified as prohibited therapies in the protocol, all therapies were to be authorized, including basic skin care (cleansing and bathing), moisturizers, bleach baths, stable antihistamines, and stable topical corticosteroids. Stable gabapentin and pregabalin were allowed as well.
As judged appropriate by the Investigator and following discussion with the medical monitor, rescue therapies included the following treatments: 1) Antihistamines (new or increased dose): for those given "as needed" at baseline, rescue of antihistamine was defined as that with an increase by ≥75% in the total weekly dose relative to the dose during the last week of screening administered for ≥1 week; 2) Gabapentin (new or increased dose) administered for ≥1 week; 3) Selected opioids: nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine): 1 or more doses; and 4) Ultraviolet radiation therapy: 1 or more treatments.

Evidence for comparator:

Placebo

Actual start date of recruitment	15 December 2021
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	Poland: 8
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	United States: 225
Worldwide total number of subjects	258
EEA total number of subjects	33

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)	175
From 65 to 84 years	79
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 487 subjects were screened at 57 study sites and 258 subjects were randomized at 53 study sites: 3 in Hungary, 2 in Poland, 8 in Spain and 40 in the USA.

Pre-assignment

Screening details:

All participants were age ≥18 years at the screening visit with ESKD and on hemodialysis 3 times per week for at least 3 months prior to the start of screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nemolizumab 30 mg

Arm description:

Participants randomized to receive 60 mg nemolizumab as a loading dose at baseline, and 30 mg nemolizumab and placebo at Week 4 and 8.

Arm type	Experimental
Investigational medicinal product name	Nemolizumab
Investigational medicinal product code	CD14152
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab was administrated subcutaneous as 2 injections (30 mg + 30 mg) at baseline (loading dose) and 1 injection at Weeks 4 and 8.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

30 mg of nemolizumab placebo were administrated as a subcutaneous injection at Weeks 4 and 8.

Arm title	Nemolizumab 60 mg

Arm description:

Participants randomized to receive 60 mg nemolizumab at baseline and at Week 4 and 8.

Arm type	Experimental
Investigational medicinal product name	Nemolizumab
Investigational medicinal product code	CD14152
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab was administrated subcutaneous as 2 injections (30 mg + 30 mg) at baseline and at Weeks 4 and 8.

Arm title	Placebo

Arm description:

Participants randomized to receive 60 mg placebo at baseline and at Week 4 and 8.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg of nemolizumab placebo were administrated as 2 subcutaneous injections at baseline and Weeks 4 and 8.

Number of subjects in period 1	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo
Started	88	85	85
Completed	72	71	72
Not completed	16	14	13
Adverse event, serious fatal	4	4	5
Consent withdrawn by subject	5	3	4
Physician decision	1	-	-
Adverse event, non-fatal	1	3	3
Not specified	3	2	-
Lost to follow-up	2	1	1
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Nemolizumab 30 mg
Reporting group description:	
Participants randomized to receive 60 mg nemolizumab as a loading dose at baseline, and 30 mg nemolizumab and placebo at Week 4 and 8.	
Reporting group title	Nemolizumab 60 mg
Reporting group description:	
Participants randomized to receive 60 mg nemolizumab at baseline and at Week 4 and 8.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive 60 mg placebo at baseline and at Week 4 and 8.	

Reporting group values	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo
Number of subjects	88	85	85
Age categorical Units: Subjects			
Adults (18-64 years)	61	53	61
From 65-84 years	26	30	23
85 years and over	1	2	1
Age continuous Units: years			
arithmetic mean	58.3	59.0	58.4
standard deviation	± 12.99	± 13.00	± 11.98
Gender categorical Units: Subjects			
Female	41	39	29
Male	47	46	56

Reporting group values	Total		
Number of subjects	258		
Age categorical Units: Subjects			
Adults (18-64 years)	175		
From 65-84 years	79		
85 years and over	4		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	109		
Male	149		

End points

End points reporting groups

Reporting group title	Nemolizumab 30 mg
Reporting group description:	
Participants randomized to receive 60 mg nemolizumab as a loading dose at baseline, and 30 mg nemolizumab and placebo at Week 4 and 8.	
Reporting group title	Nemolizumab 60 mg
Reporting group description:	
Participants randomized to receive 60 mg nemolizumab at baseline and at Week 4 and 8.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive 60 mg placebo at baseline and at Week 4 and 8.	

Primary: Proportion of subjects with an improvement in WI NRS ≥4

End point title	Proportion of subjects with an improvement in WI NRS ≥4
End point description:	
Proportion of subjects with an improvement in Worst Itch Numeric Rating Scale (WI NRS) ≥4 from baseline at Week 12 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug	
End point type	Primary
End point timeframe:	
From Baseline by Week 12	

End point values	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	85	85	
Units: percent				
number (not applicable)				
Improvement of ≥4 from baseline in WI NRS	38.5	47.7	32.4	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Strata-adjusted differences in proportions (nemolizumab - placebo) were obtained from CMH after adjusting for analysis center. 97.5% CI were based on the large sample approximation method for binary data using Mantel-Haenszel strata weights and the Sato variance estimator. Rubin's Method was used to pool results of 50 multiply imputed datasets.	
Comparison groups	Nemolizumab 30 mg v Placebo

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3696 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted proportion difference
Point estimate	7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-10.6
upper limit	24.6

Notes:

[1] - p-value for the combined CMH test was obtained as the upper-tailed p-value from the t-test produced by PROC MIANALYZE on the pooled standardized Wilson-Hilferty transformed CMH statistic.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Strata-adjusted differences in proportions (nemolizumab - placebo) were obtained from CMH after adjusting for analysis center. 97.5% CI were based on the large sample approximation method for binary data using Mantel-Haenszel strata weights and the Sato variance estimator. Rubin's Method was used to pool results of 50 multiply imputed datasets.

Comparison groups	Nemolizumab 60 mg v Placebo
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0686 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted proportion difference
Point estimate	14.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.1
upper limit	32.2

Notes:

[2] - p-value for the combined CMH test was obtained as the upper-tailed p-value from the t-test produced by PROC MIANALYZE on the pooled standardized Wilson-Hilferty transformed CMH statistic.

Secondary: Proportion of subjects with an improvement

End point title	Proportion of subjects with an improvement

End point description:

Improvement in Worst Itch Numeric Rating Scale (WI NRS) and Sleep Disturbance Numerical Rating Scale (SD NRS)

End point type	Secondary

End point timeframe:

From Baseline to Week 4 or Week 12

End point values	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	85	85	
Units: percent				
number (not applicable)				
Improvement in WI NRS ≥3 from baseline at Week 12	49.3	60.6	47.1	
Improvement in WI NRS ≥4 from baseline at Week 4	24.3	26.6	7.4	
Improvement in SD NRS ≥4 from baseline at Week 12	27.7	42.6	25.3	
Improvement in WI NRS ≥3 from baseline at Week 4	36.5	35.0	12.8	
Improvement in SD NRS ≥4 from baseline at Week 4	16.1	23.6	2.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the Baseline till the last follow up study visit (Week 20)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Nemolizumab 30 mg
Reporting group description:	
Participants randomized to receive 60 mg nemolizumab as a loading dose at baseline, and 30 mg nemolizumab and placebo at Week 4 and 8.	
Reporting group title	Nemolizumab 60 mg
Reporting group description:	
Participants randomized to receive 60 mg nemolizumab at baseline and at Week 4 and 8.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive 60 mg placebo at baseline and at Week 4 and 8.	

Serious adverse events	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 86 (38.37%)	22 / 84 (26.19%)	27 / 85 (31.76%)
number of deaths (all causes)	4	4	5
number of deaths resulting from adverse events	4	4	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign renal neoplasm			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear cell papillary renal cell carcinoma			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Triple negative breast cancer			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Surgical and medical procedures			
Renal transplant			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access placement			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney transplant rejection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver transplant rejection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	0 / 86 (0.00%)	2 / 84 (2.38%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (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 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous graft thrombosis			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	0 / 85 (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
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula maturation failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haematoma			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft occlusion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	4 / 86 (4.65%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery aneurysm			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery dissection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			

subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 86 (1.16%)	2 / 84 (2.38%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 3
Cardiac failure congestive			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Metabolic encephalopathy			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	0 / 85 (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
Post cardiac arrest syndrome			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	5 / 85 (5.88%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	0 / 85 (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	1 / 86 (1.16%)	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abscess limb			

subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial myositis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis orbital			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall abscess			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			

subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis bacterial			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Device related sepsis			

subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enterococcal bacteraemia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	4 / 86 (4.65%)	1 / 84 (1.19%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	3 / 86 (3.49%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Nemolizumab 30 mg	Nemolizumab 60 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 86 (33.72%)	25 / 84 (29.76%)	19 / 85 (22.35%)
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	2	0	1
Dialysis hypotension			
subjects affected / exposed	0 / 86 (0.00%)	3 / 84 (3.57%)	1 / 85 (1.18%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	3 / 86 (3.49%)	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences (all)	3	1	2
Cough			
subjects affected / exposed	0 / 86 (0.00%)	3 / 84 (3.57%)	2 / 85 (2.35%)
occurrences (all)	0	3	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 86 (3.49%)	0 / 84 (0.00%)	3 / 85 (3.53%)
occurrences (all)	3	0	3
Arteriovenous fistula site complication			
subjects affected / exposed	3 / 86 (3.49%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences (all)	3	0	0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 86 (0.00%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 86 (3.49%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 86 (3.49%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	3	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 86 (2.33%)	2 / 84 (2.38%)	2 / 85 (2.35%)
occurrences (all)	2	2	2
Eosinophilia			
subjects affected / exposed	1 / 86 (1.16%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	1	2	0
Polycythaemia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	3 / 86 (3.49%)	3 / 84 (3.57%)	3 / 85 (3.53%)
occurrences (all)	3	3	3
Diarrhoea			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	4 / 85 (4.71%)
occurrences (all)	1	1	4
Toothache			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	2	1	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 86 (0.00%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 86 (2.33%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	2	2	0
Muscle spasms			
subjects affected / exposed	1 / 86 (1.16%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	1	2	0
Pain in extremity			
subjects affected / exposed	0 / 86 (0.00%)	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	0	2	1
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	2	1	1
Urinary tract infection			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	2	1	0
COVID-19			

subjects affected / exposed	1 / 86 (1.16%)	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	1	2	1
Nasopharyngitis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	2	0	2
Bronchitis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	2	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	3 / 86 (3.49%)	4 / 84 (4.76%)	3 / 85 (3.53%)
occurrences (all)	3	4	3
Hypervolaemia			
subjects affected / exposed	1 / 86 (1.16%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	1	2	0
Hyperglycaemia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	0	2	1
Hypocalcaemia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2022	Protocol, version 2.0 • Reduced the threshold for conditional power of interim study stopping rule • Clarified the unblinded PK/PD group for the interim analysis • Clarified PEF and ACT testing • Added language for abnormal liver laboratory findings to incorporate Hy's law in applicable protocol sections • Updated the device on which subjects would complete the WI NRS and SD NRS (i.e., changed from paper form to an ePRO device) • Updated the schedule of assessments with respect to eDiary, full physical examinations, 12-lead ECG, blood sample collection for hematology and biochemistry, urinalysis, ACT, and PEF • Deleted mention that electrocardiogram machines would be provided • Clarified that descriptive statistics would be calculated for all individual popPK derived parameters • Designated the CRO and that an unblinded group would be used for the interim analysis • Updated the website for the Centers for Disease Control
11 March 2022	Protocol, version 3.0 • Removed exclusion criterion 8d (pertained to PEF) • Described PEF as supplemental information as opposed to an exclusion criterion • Updated the schedule of assessments footnotes to capture PEF testing and deleted a repetitious footnote • Clarified the AESI of new asthma—that reduction in PEF value needed to be sent to adjudication only if there were suggestive asthma signs and/or symptoms and absence of another disease as a cause
08 June 2022	Protocol, version 4.0 • Allowed enrollment of subjects who had CKD with moderate pruritus • Changed inclusion criterion 3 to reflect that 60 days is a suitable duration to cover 2 single-pool Kt/V measurements as opposed to 45 days • Decreased the WI NRS score from ≥7.0 to ≥5.0 in inclusion criterion 5 and provided the rationale for this change • Changed wording describing WI NRS from "reduction" to "improvement" • Adjusted ranges in subgroup analyses to accommodate moderate pruritus • Allowed rescheduling up to 72 hours from the screening window in exceptional circumstances • Allowed for subjects who failed prior to Protocol Version 4.0 to rescreen if their WI NRS was ≥5.0

07 February 2023	Protocol, version 5.0 • Updated the Sponsor's address • Removed the interim analysis • Allowed seasonal, emergency, and COVID vaccines • Further described the details of the estimand for the primary efficacy endpoints and further clarified how the intake of rescue therapy would be included in the definition of the binary composite response • Provided more detail for the WI NRS/SD NRS calculation • Corrected the multiplicity adjustment for primary and key secondary efficacy endpoints • Clarified the handling of missing data, added sensitivity analyses for the primary endpoint, and defined the mITT, PP and observed case analyses as supplementary (rather than sensitivity) as per ICH E9 (R1) addendum on estimands and sensitivity analysis • Specified that dose selection would be based on the final analysis, as the interim analysis was removed • Specified that the impact of body weight on efficacy would be evaluated at the end of the study • Added IGA of CKD-aP skin status to unscheduled visit(s) in the schedule of assessments • Provided an EMEA email address for reporting an AESI, SAE, or pregnancy
21 September 2023	Protocol, version 6.0 • Added the biostatistician as an approver • Updated primary efficacy estimand and attributes to address treatment discontinuation due to lack of efficacy or adverse event/death related to study drug • Corrected the follow-up visit window • Clarified that missing data for dichotomous efficacy endpoints would be imputed using multiple imputations under missing at random assumption for the primary/main analyses; 'non-responder' imputation would be used as a sensitivity analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported