Clinical trial results:
Safety, Tolerability and Efficacy of anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Rejection after Kidney Transplantation - A Pilot Trial

Summary

EudraCT number	2017-001604-30
Trial protocol	AT DE
Global end of trial date	09 April 2020

Results information

Result version number	v1 (current)
This version publication date	07 May 2022
First version publication date	07 May 2022

Trial information

Trial identification

Sponsor protocol code	1001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03444103
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité Berlin
Sponsor organisation address	Charitépl. 1, Berlin, Germany, 10117
Public contact	Office-Dept. Clinical Pharmacology, Medical University of Vienna, +43 1 404002981, klin-pharmakologie@meduniwien.ac.at
Scientific contact	Office-Dept. Clinical Pharmacology, Medical University of Vienna, +43 1 404002981, klin-pharmakologie@meduniwien.ac.at
Sponsor organisation name	Medizinische Universität Wien
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Prof. Dr. Georg Böhmig, Medical University of Vienna, georg.boehmig@meduniwien.ac.at
Scientific contact	Prof. Dr. Georg Böhmig, Medical University of Vienna, georg.boehmig@meduniwien.ac.at

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	09 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate safety and tolerability of Interleukin-6 blockade by clazakizumab in kidney transplant recipients on baseline immunosuppresion.

Protection of trial subjects:

The study was approved by the institutional review board of the Medical University of Vienna (EK1428/2017), the Berlin State Ethics Committee (17/0485– EK 15), and the regulatory authorities in Austria (Federal Office for Safety in Health Care, Austrian Agency for Health and Food Safety) and Germany (Federal Institute for Vaccines and Biomedicines, Paul-Ehrlich Institute). All patients provided written informed consent before study inclusion, and the study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice requirements, Good Laboratory Practice, the principles of the Declaration of Helsinki 2008, and the Declaration of Istanbul. Adverse events were closely monitored throughout the study and classified using the Medical Dictionary for Regulatory Activities Version 23.0. The study was monitored by an independent data and safety monitoring board (DSMB), and included two interim analyses, the first after 10 and the second after 20 subjects had completed part Aof the study. The DSMB was instructed to consider stopping the trial if the pattern of related serious adverse events or safety laboratory results strongly supported a major safety signal.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period was January 2018 to April 2019.

Pre-assignment

Screening details:

22 Donor-specific antibody-positive kidney transplant recipients were assessed for eligibility.
2 Were not eligible.

Period 1

Period 1 title	Part A of the trial
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

Study participants, care providers, and those assessing outcomes were unaware of the randomization sequence. The allocation sequencewas generated, and medication or placebowas prepared by independent nonblinded study pharmacists. Study physicians and nurses were provided with blinded subcutaneous medication. The participating investigators, staff with medical interaction, and the study participants were blinded to group allocation until the last patient had completed part A.

Arms

Are arms mutually exclusive?	Yes
Arm title	Clazakizumab Group

Arm description:

Clazakizumab is a humanized monoclonal IgG1 antibody with high affinity for IL-6 and a long t1/2 of approximately 30 days. This antibody has been systematically evaluated in rheumatoid and psoriatic arthritis.

Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab (25 mg in 1 ml single-dose vials) were administered via subcutaneous injection in 4-weekly intervals. After amendment dosage reduced to 12.6mg per injection.

Arm title	Placebo

Arm description:

placebo (0.9% saline)

Arm type	Placebo
Investigational medicinal product name	Isotonische Kochsalzlösung Fresenius Infusionslösung
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

placebo (0.9% saline) were administered via subcutaneous injection in 4-weekly intervals

Number of subjects in period 1	Clazakizumab Group	Placebo
Started	10	10
Completed	9	10
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Part B of the trail
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	clazakizumab (all) Group

Arm description:

a 40-week open-label extension where all participants received clazakizumab (part B). The rationale behind this design was to offer all participants the option of a potentially effective treatment.

Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab (12.6 mg in 1 ml single-dose vials) were administered via subcutaneous injection in 4-weekly intervals.

Number of subjects in period 2	clazakizumab (all) Group
Started	19
Completed	18
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Clazakizumab Group
Reporting group description:	
Clazakizumab is a humanized monoclonal IgG1 antibody with high affinity for IL-6 and a long t1/2 of approximately 30 days. This antibody has been systematically evaluated in rheumatoid and psoriatic arthritis.	
Reporting group title	Placebo
Reporting group description:	
placebo (0.9% saline)	

Reporting group values	Clazakizumab Group	Placebo	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	10	19
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous Units: years			
median	47.2	39.6	
inter-quartile range (Q1-Q3)	38.7 to 62.1	30.2 to 59.6	-
Gender categorical Units: Subjects			
Female	3	7	10
Male	7	3	10
DSA characterisstics Units: Subjects			
HLA class I DSA only,	1	1	2
HLA class II DSA only	7	7	14
HLA class I and II DSA	2	2	4
DSA characteristics Units: Subjects			
Anti-DQ DSA	7	8	15
no anti-DQ DSA	3	2	5
Variables recorded at trial inclusion: duration until inlcusion			
Years to inclusion in the trial			
Units: Years			
median	9.7	11.4	
inter-quartile range (Q1-Q3)	4.1 to 16.7	5.9 to 16.1	-

Variables recorded at trial inclusion eGFR			
Units: ml/min			
median	40.5	39.2	
inter-quartile range (Q1-Q3)	33.3 to 49.8	32.9 to 51.7	-
Variables recorded at trial inclusion: Protein/creatinine ratio			
Units: mg/g			
median	727	1387	
inter-quartile range (Q1-Q3)	197 to 1311	532 to 3575	-
DSA characteristics: MFI of the peak DSA			
Units: Intensity			
median	10789	14207	
inter-quartile range (Q1-Q3)	3092 to 15437	1252 to 19144	-
DSA characteristics: MFI sum of detected			
Units: Intensity			
median	10789	16126	
inter-quartile range (Q1-Q3)	4244 to 18102	1252 to 19302	-

End points

End points reporting groups

Reporting group title	Clazakizumab Group
Reporting group description:	
Clazakizumab is a humanized monoclonal IgG1 antibody with high affinity for IL-6 and a long t1/2 of approximately 30 days. This antibody has been systematically evaluated in rheumatoid and psoriatic arthritis.	
Reporting group title	Placebo
Reporting group description:	
placebo (0.9% saline)	
Reporting group title	clazakizumab (all) Group
Reporting group description:	
a 40-week open-label extension where all participants received clazakizumab (part B). The rationale behind this design was to offer all participants the option of a potentially effective treatment.	

Primary: Safty: overall AEs during Part A and B

End point title	Safty: overall AEs during Part A and B
End point description:	
This phase 2 pilot trial, the first randomized controlled trial evaluating IL-6 signaling blockade in transplantation, assessing the safety and tolerability. For more details see category Adverse Events	
End point type	Primary
End point timeframe:	
51 Weeks	

End point values	Clazakizumab Group	Placebo	clazakizumab (all) Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	19	
Units: Events				
Adverse Event	50	44	129	
serious AE	3	1	9	
non-serious AEs	47	43	120	

Statistical analyses

Statistical analysis title	group comparisons
Comparison groups	Clazakizumab Group v Placebo v clazakizumab (all) Group

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	t-test, 2-sided

Notes:

[1] - Intergroup differences were tested at a two-sided significance level of 5%. For statistical analysis, IBM SPSS Statistics version 24.

Secondary: Efficacy: HLA Antibody and Ig Levels

End point title	Efficacy: HLA Antibody and Ig Levels

End point description:

Comparison to baseline. Extension of treatment in part B led to a further decrease of DSA levels (P,0.001) see attchment: DSAlvls

End point type	Secondary

End point timeframe:

51 weeks

End point values	Clazakizumab Group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Percentage				
median (inter-quartile range (Q1-Q3))				
DSA MFI	77 (63 to 101)	103 (94 to 104)		

Attachments (see zip file)	DSA lvls/DSAlvls.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of Rejection: the changes in ABMR

End point title	Evolution of Rejection: the changes in ABMR

End point description:

ABMR,antibody-mediated rejection; significant intergroup differences in rejection-relatedmolecular and morphologic scores see attachment: Evolution of Rejection

End point type	Secondary

End point timeframe:

51 weeks

End point values	clazakizumab (all) Group			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
negative ABMR score	7			
resolution of ABMR activity	4			
disappearance of capillary C4d deposits	5			

Attachments (see zip file)	Evolution of Rejection/Evolution of Rejection.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: slowed eGFR decline

End point title	slowed eGFR decline

End point description:

Kidney allograft function: The individual course of eGFR shown in attachment

End point type	Secondary

End point timeframe:

51 weeks

End point values	Clazakizumab Group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ml/min/mm²				
arithmetic mean (confidence interval 95%)				
Part A eGFR	-0.96 (-1.96 to 0.03)	-2.43 (-3.40 to -1.46)		
Part B eGFR	-0.29 (-0.85 to 0.26)	-0.64 (-1.13 to -0.14)		

Attachments (see zip file)	Kidney allograft function/F5.large.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 51 Weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Part A clazakizumab
Reporting group description: -	
Reporting group title	Part A Placebo
Reporting group description: -	
Reporting group title	Part B clazakizumab
Reporting group description: -	

Serious adverse events	Part A clazakizumab	Part A Placebo	Part B clazakizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	1 / 10 (10.00%)	7 / 19 (36.84%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events		0	0
Surgical and medical procedures			
Pleurodesis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Permanent thorax cavity drainage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute renal injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (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

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

Non-serious adverse events	Part A clazakizumab	Part A Placebo	Part B clazakizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	18 / 19 (94.74%)
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	3 / 19 (15.79%)
occurrences (all)	2	3	3
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Deep vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Mole excision			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Nasal septum operation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Permanent thorax cavity drainage			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pleurodesis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	6 / 19 (31.58%)
occurrences (all)	2	3	6
Injection site reactions			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	3
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Malaise			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Dyspnea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	3

Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nasal dryness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Small airway disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Sleep disturbance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Transplant biopsy complication			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	0 / 19 (0.00%)
occurrences (all)	1	2	0
Traumatic bone or joint injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Bradycardia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	4 / 19 (21.05%)
occurrences (all)	0	3	4
Numbness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Ocular infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 10 (40.00%)	3 / 10 (30.00%)	6 / 19 (31.58%)
occurrences (all)	4	3	6
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	0 / 19 (0.00%)
occurrences (all)	2	3	0
Gastroenenteritis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	2	2
Nausea and/or vomiting			

subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	2 / 19 (10.53%)
occurrences (all)	0	2	2
Diverticulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Aphtous ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Noninfective gingivitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pancreatic enzyme abnormality			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Erysipela			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1

Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Blister			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hirsutism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Impetigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Intertrigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute renal injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Aggravated proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	3 / 19 (15.79%)
occurrences (all)	2	1	3
Muscle cramps			
subjects affected / exposed	3 / 10 (30.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	3	1	1
Tenosynovitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 10 (50.00%)	6 / 10 (60.00%)	8 / 19 (42.11%)
occurrences (all)	5	6	8
Urethritis and/or cystitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	3 / 19 (15.79%)
occurrences (all)	1	2	3
Bronchitis fungal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	4 / 19 (21.05%)
occurrences (all)	0	0	4
Herpes simplex			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	3
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Aseptic meningitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Coxsackie viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ovarian abscess			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pyelonephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Folate deficiency			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hyperkalemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2019	changes in the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33443079