Clinical trial results:
suPAR-GUIDED ANAKINRA TREATMENT FOR VALIDATION OF THE RISK AND EARLY MANAGEMENT OF SEVERE RESPIRATORY FAILURE BY COVID-19: THE SAVE-MORE DOUBLE-BLIND, RANDOMIZED, PHASE III CONFIRMATORY TRIAL

Summary

EudraCT number	2020-005828-11
Trial protocol	GR IT
Global end of trial date	28 June 2021

Results information

Result version number	v1 (current)
This version publication date	01 February 2024
First version publication date	01 February 2024

Trial information

Trial identification

Sponsor protocol code	SAVE-MORE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04680949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Institute for the Study of Sepsis
Sponsor organisation address	Laodikeias 17 str., Athens, Greece, 11528
Public contact	President of the Board, Hellenic Institute for the Study of Sepsis, 0030 2107480662, info@sepsis.gr
Scientific contact	President of the Board, Hellenic Institute for the Study of Sepsis, 0030 2107480662, info@sepsis.gr

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	16 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The SAVE-MORE is a pivotal, confirmatory, phase III randomized clinical trial (RCT) aiming to evaluate the efficacy and safety of early start of anakinra guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO clinical progression scale (CPS).

Protection of trial subjects:

Patients were hospitalized during the trial and were closely monitored by follow-up calls when discharged until the completion of the trial period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 December 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 528
Country: Number of subjects enrolled	Italy: 66
Worldwide total number of subjects	594
EEA total number of subjects	594

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)	344

From 65 to 84 years	238
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

The study was performed in 37 research sites, 29 in Greece and 8 in Italy. Recruitment begun from 27 December 2020 and the follow up period was concluded at 28 June 2021. In total, 606 patients were enrolled (194 patients in Treatment Arm 1 and 412 in Treatment arm 2).

Pre-assignment

Screening details:

A set of inclusion criteria needed to be met for patient enrolment, including confirmed SARS-CoV-2 infection and suPAR level over 6 ng/ml among others. Patients who met any of the exclusion criteria were not enrolled in the study.

Pre-assignment period milestones

Number of subjects started	594
Number of subjects completed	594

Period 1

Period 1 title	Follow-Up Day 28
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator
Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 1	Treatment Arm 1	Treatment Arm 2
Started	189	405
Completed	189	405

Period 2

Period 2 title	Follow-Up Day 14
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator

Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 2	Treatment Arm 1	Treatment Arm 2
Started	189	405
Completed	189	405

Period 3

Period 3 title	Follow-Up Day 7 - Hospitalized
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator

Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 3	Treatment Arm 1	Treatment Arm 2
Started	189	405
Completed	184	392
Not completed	5	13
No longer hospitalized	5	13

Period 4

Period 4 title	Follow-Up Day 60
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator

Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 4[1]	Treatment Arm 1	Treatment Arm 2
Started	183	392
Completed	183	392

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: The number of patients in the period in question (Follow-Up Day 60) is lower since several patients were lost to follow-up. More precisely, for Follow-up Day 60, the data of 183 Patients of Arm1, and 392 Patients of Arm 2 were available i.e. 6 and 14 patients respectively were lost to follow-up.

Period 5

Period 5 title	Follow-Up Day 90
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator

Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 5[2]	Treatment Arm 1	Treatment Arm 2
Started	179	388
Completed	179	388

Notes:

[2] - 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: The number of patients in the period in question (Follow-Up Day 90) is lower since several patients were lost to follow-up. More precisely, for Follow-up Day 60, the data of 179 Patients of Arm1, and 388 Patients of Arm 2 were available i.e. 10 and 16 patients respectively were lost to follow-up.

Period 6

Period 6 title	Follow-Up Day 14 - Hospitalized
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator

Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 6[3]	Treatment Arm 1	Treatment Arm 2
Started	66	120
Completed	66	120

Notes:

[3] - 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: According to the statistical analysis plan, this variable is analysed only for patients still hospitalised by Day 14. The reason is that for patients who had been discharged from the hospital before Day 14, the SOFA score cannot be calculated.

Period 7

Period 7 title	Follow-Up Intensive care unit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo was administered using syringes of the same appearance as the anakinra syringes. All syringes were prepared by the unblinded pharmacist for s.c. injection. The outer part of each syringe was covered to conceal the identity of the study drug, labelled with a unique alphanumeric code, and delivered to the blinded pharmacist and nurse for administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1

Arm description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

0.67 ml s.c. once daily

Arm title	Treatment Arm 2

Arm description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Arm type	Active comparator

Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg s.c once daily

Number of subjects in period 7[4]	Treatment Arm 1	Treatment Arm 2
Started	31	39
Completed	31	39

Notes:

[4] - 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: This period included only the patients who were admitted in the ICU. No patients were in the ICU at baseline. Overall, 31 (16.4%) patients in Arm 1 were admitted in the ICU compared to 39 (9.6%) patients in Arm 2.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Arm 1
Reporting group description:	
0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days	
Reporting group title	Treatment Arm 2
Reporting group description:	
Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days	

Reporting group values	Treatment Arm 1	Treatment Arm 2	Total
Number of subjects	189	405	594
Age categorical Units: Subjects			
Adults (18-64 years)	111	233	344
From 65-84 years	75	163	238
85 years and over	3	9	12
Age continuous			
The mean age of patients in the FAS was 61.9 years			
Units: years			
arithmetic mean	61.5	62	
standard deviation	± 11.3	± 11.4	-
Gender categorical			
57.9% of patients were male and 42.1% were female.			
Units: Subjects			
Female	81	169	250
Male	108	236	344
WHO classification for COVID-19 at the time of screening Units: Subjects			
Moderate pneumonia	27	82	109
Severe pneumonia	162	323	485
WHO classification for COVID-19 before start of the study drug Units: Subjects			
Moderate pneumonia	12	39	51
Severe pneumonia	177	366	543
Comorbidities Units: Subjects			
Type 2 diabetes mellitus	28	66	94
Chronic heart failure	5	13	18
Chronic renal disease	1	9	10
Chronic obstructive pulmonary disease	9	15	24
Coronary heart disease	13	28	41
Atrial fibrillation	8	20	28
Depression	9	25	34
None	116	229	345
Use of oxygen at screening			
Disposition of the use of oxygen at screening			

Units: Subjects			
Moderate patients hospitalized without oxygen	27	82	109
Severe patients hospitalized in need of oxygen	162	323	485
Use of oxygen at randomization			
Disposition of the use of oxygen at randomization			
Units: Subjects			
Patients hospitalized without oxygen	12	39	51
Patients hospitalized with oxygen	177	366	543
Co-administered Remdesivir Units: Subjects			
Yes	141	298	439
No	48	107	155
Co-administered Dexamethasone at enrollment Units: Subjects			
Yes	160	326	486
No	29	79	108
Co-administered Dexamethasone over follow-up due to progression from moderate to severe disease Units: Subjects			
Yes	8	16	24
No	181	389	570
Co-administered low molecular weight heparin Units: Subjects			
Yes	175	385	560
No	14	20	34
Co-administered β-lactamase inhibitors Units: Subjects			
Yes	10	23	33
No	179	382	561
Co-administered Piperacillin/tazobactam Units: Subjects			
Yes	36	64	100
No	153	341	494
Co-administered Ceftriaxone Units: Subjects			
Yes	85	155	240
No	104	250	354
Co-administered Ceftaroline Units: Subjects			
Yes	32	75	107
No	157	330	487
Co-administered respiratory fluoroquinolone Units: Subjects			
Yes	24	53	77
No	165	352	517
Co-administered Azithromycin Units: Subjects			

Yes	35	76	111
No	154	329	483
Co-administered any glycopeptide Units: Subjects			
Yes	19	24	43
No	170	381	551
Co-administered linezolid Units: Subjects			
Yes	22	45	67
No	167	360	527
Body mass index			
Mean body mass index (BMI) was 29.5 for the FAS.			
Units: Number			
arithmetic mean	29.8	29.4	
standard deviation	± 5.6	± 5.5	-
Charlson’s comorbidity index Units: Number			
arithmetic mean	2.2	2.3	
standard deviation	± 1.5	± 1.6	-
SOFA score			
Sequential Organ Failure Assessment score ranging from 0 to 24			
Units: Number			
arithmetic mean	2.5	2.4	
standard deviation	± 1.2	± 1.1	-
Days to start of study drug from symptom onset Units: Number			
median	9	9	
inter-quartile range (Q1-Q3)	7 to 11	7 to 12	-
Days to start of study drug from hospital admission Units: Number			
median	2	2	
inter-quartile range (Q1-Q3)	2 to 3	2 to 3	-
White blood cell count			
cells per mm3			
Units: Number			
median	5910	5980	
inter-quartile range (Q1-Q3)	4280 to 8300	4320 to 8180	-
Lymphocyte count			
Cells per mm3			
Units: number			
median	730	815	
inter-quartile range (Q1-Q3)	560 to 1090	570 to 1110	-
C-reactive protein			
mg/litre			
Units: mg/litre			
median	51.4	50.5	
inter-quartile range (Q1-Q3)	25.2 to 97.9	25.3 to 100.9	-
Interleukin-6 Units: pg/ml			
median	20.1	15.5	

inter-quartile range (Q1-Q3)	7.4 to 44.9	6.6 to 39.3	-
Ferritin			
Units: ng/mL			
median	628.6	558.9	
inter-quartile range (Q1-Q3)	293.5 to 1062.3	294.1 to 1047	-
Serum soluble uPAR			
Units: ng/mL			
median	7.5	7.6	
inter-quartile range (Q1-Q3)	6.9 to 9.3	7 to 9.1	-
D-dimers			
Units: mg/L			
median	0.51	0.52	
inter-quartile range (Q1-Q3)	0.31 to 0.92	0.30 to 1.0	-
PO2:FiO2			
Units: mmHg			
median	215	235	
inter-quartile range (Q1-Q3)	161 to 293	178 to 304	-
Administered doses of study drug			
Units: Number			
arithmetic mean	8.7	8.4	
standard deviation	± 2.0	± 2.1	-

End points

End points reporting groups

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 1

Reporting group description:

0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days

Reporting group title	Treatment Arm 2

Reporting group description:

Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days

Primary: Efficacy of early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

End point title	Efficacy of early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

End point description:

Efficacy of early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

End point type	Primary

End point timeframe:

28 Days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	405		
Units: Individuals				
Fully recovered PCR (-)	50	204		
Asymptomatic PCR (+)	6	40		
Symptomatic independent	74	93		
Symptomatic assistance needed	21	25		
Hospitalized no need for oxygen	3	9		
Hospitalized with nasal/mask oxygen	10	8		
Need for HFO or NIV	1	1		
Mechanical ventilation with P/F >150	1	1		
Mechanical ventilation with P/F <150 or vasopre	4	5		
Mechanical ventilation with P/F <150 and vasopr	6	6		
Dead	13	13		

Attachments (see zip file)	Study primary outcome - WHO-CPS at Day 28 - FAS/Study

Statistical analyses

Statistical analysis title	Ordinal logistic regression

Statistical analysis description:

Multivariate ordinal regression was the primary statistical analysis procedure followed. The basic assumption of the model was the assumption of proportional odds (also called the assumption of parallel lines), which was checked by performing the relevant chi-square test and the goodness-of-fit test reported through Pearson’s chi-square test. The dependent variable was the 11-point WHO CPS scale, and the primary independent variable was the arm of treatment.

Comparison groups	Treatment Arm 1 v Treatment Arm 2

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001 [2]
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.5

Notes:

[1] - Null hypothesis testing

[2] - p value has reached p<0.0001

Secondary: Supporting analysis of the WHO-CPS at Day 14

End point title	Supporting analysis of the WHO-CPS at Day 14

End point description:

The first supporting analysis of the WHO-CPS at Day 14 is to assess whether anakinra can demonstrate benefit earlier than Day 28.

End point type	Secondary

End point timeframe:

14 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	405		
Units: Individuals				
Fully recovered PCR (-)	8	25		
Asymptomatic PCR (+)	17	82		
Symptomatic independent	70	139		
Symptomatic assistance needed	21	35		
Hospitalized no need for oxygen	17	42		
Hospitalized with nasal/mask oxygen	29	55		
Need for HFO or NIV	4	5		
Mechanical ventilation with P/F >150	4	2		
Mechanical ventilation with P/F <150 or vasopre	8	11		
Mechanical ventilation with P/F <150 and vasopr	7	9		
Dead	4	0		

Attachments (see zip file)	WHO-CPS at Day 14 - FAS population/Supportive analysis of

Statistical analyses

Statistical analysis title	Ordinal regression
Statistical analysis description:	
The adjusted OR after multivariate analysis was 0.58 (95% CI: 0.42 to 0.79; p<0.001).	
Comparison groups	Treatment Arm 1 v Treatment Arm 2
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.79

Notes:

[3] - Null hypothesis testing

Secondary: Change of the WHO-CPS at Day 28	
End point title	Change of the WHO-CPS at Day 28
End point description:	
Ordinal regression analysis showing that anakinra treatment reduced the 11-point WHO-CPS at Day 28 from baseline Day 1 .	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	405		
Units: points				
median (inter-quartile range (Q1-Q3))	-3 (-4.5 to -2)	-4 (-5 to -3)		

Attachments (see zip file)	Absolute change of WHO-CPS at Day 28/Absolute change of

Statistical analyses

Statistical analysis title	Ordinal logistic regression
Statistical analysis description:	
Covariates entered in the multivariate model were those used for stratified randomization. The ordinal regression analysis showed that anakinra treatment reduced the 11-point WHO-CPS at Day 28 compared to placebo (OR: 0.40; 95% CI: 0.29-0.55; p<0.0001).	
Comparison groups	Treatment Arm 1 v Treatment Arm 2

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.55

Notes:

[4] - Null hypothesis testing

Secondary: Change of the WHO-CPS at Day 14

End point title	Change of the WHO-CPS at Day 14

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	405		
Units: points				
median (inter-quartile range (Q1-Q3))	-2 (-3 to 0)	-3 (-3 to -1)		

Attachments (see zip file)	Absolute change of WHO-CPS at Day 14/Absolute change of

Statistical analyses

Statistical analysis title	Ordinal logistic regression

Statistical analysis description:

Covariates entered in the multivariate model were those used for stratified randomization. The ordinal regression analysis showed that anakinra treatment reduced the 11-point WHO-CPS at Day 14 compared to placebo (OR: 0.63; 95% CI: 0.46 to 0.86; p=0.003).

Comparison groups	Treatment Arm 1 v Treatment Arm 2

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.003 [6]
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.86

Notes:

[5] - Null hypothesis testing

[6] - p=0.003

Secondary: Change of the sequential organ failure assessment score by Day 14

End point title	Change of the sequential organ failure assessment score by Day 14

End point description:

The ordinal regression analysis showed a non-significant result for absolute change of SOFA score from baseline by Day 14 (OR: 0.67; 95% CI 0.39 to 1.15; p=0.150). Covariates entered in the multivariate model were those used for stratified randomization.

End point type	Secondary

End point timeframe:

14 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	120		
Units: points				
median (inter-quartile range (Q1-Q3))	0 (-1 to 2)	-1 (-2 to 1)		

Attachments (see zip file)	Absolute change of the SOFA score by Day 14 /Absolute

Statistical analyses

Statistical analysis title	Ordinal logistic regression

Statistical analysis description:

The ordinal regression analysis showed a non-significant result for absolute change of SOFA score from baseline by Day 14 (OR: 0.67; 95% CI 0.39 to 1.15; p=0.150). Covariates entered in the multivariate model were those used for stratified randomization.

Comparison groups	Treatment Arm 2 v Treatment Arm 1

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.15 [8]
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.15

Notes:

[7] - Null hypothesis testing

[8] - p=0.150 (non significant)

Secondary: Change of the sequential organ failure assessment score by Day 7

End point title	Change of the sequential organ failure assessment score by Day 7

End point description:

The ordinal regression analysis showed that anakinra treatment lead to an absolute reduction of the SOFA score by Day 7 compared to placebo (OR: 0.64; 95% CI: 0.47 to 0.88; p=0.007). Covariates entered in the multivariate model were those used for stratified randomization.

End point type	Secondary

End point timeframe:

7 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	392		
Units: points				
median (inter-quartile range (Q1-Q3))	0 (-1 to 0)	-1 (-2 to 0)		

Attachments (see zip file)	Absolute change of the SOFA score by Day 7 /Absolute change

Statistical analyses

Statistical analysis title	Ordinal logistic regression

Statistical analysis description:

The ordinal regression analysis showed that anakinra treatment lead to an absolute reduction of the SOFA score by Day 7 compared to placebo (OR: 0.64; 95% CI: 0.47 to 0.88; p=0.007). Covariates entered in the multivariate model were those used for stratified randomization.

Comparison groups	Treatment Arm 1 v Treatment Arm 2

Number of subjects included in analysis	576
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.007 [10]
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.88

Notes:

[9] - Null hypothesis testing

[10] - p=0.007

Secondary: Time until discharge from hospital

End point title	Time until discharge from hospital

End point description:

A multivariate Cox regression analysis was performed, to determine the difference to live discharge from hospital (days) taking into account the following variables:

Intake of Anakinra treatment, Severe COVID-19 by WHO classification, Dexamethasone treatment, BMI >30 kg/m2, Country (Italy/Greece)

End point type	Secondary

End point timeframe:

90 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	388		
Units: days				
median (full range (min-max))	11 (3 to 90)	10 (4 to 90)		

Attachments (see zip file)	Cox regression analysis - discharge by day 90/Cox regression

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

By Day 90, 184 (97.4%) of the 189 patients in the placebo+SoC group and 404 (99.8%) of the 405 patients in the anakinra+SoC group were discharged from the hospital or died (p=0.037) between the 2 arms of treatment by the Fisher exact test). The multivariate Cox regression analysis showed that the time until hospital discharge was 1 day shorter in the anakinra+SoC group than in the placebo+SoC group (HR: 1.26; 95% CI: 0.05 to 1.52; p=0.013).

Comparison groups	Treatment Arm 1 v Treatment Arm 2

Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.013 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	1.52

Notes:

[11] - Null hypothesis testing

[12] - p=0.013

Secondary: Time until discharge from the intensive care unit

End point title	Time until discharge from the intensive care unit

End point description:

This analysis included only the patients who were admitted in the ICU. No patients were in the ICU at baseline. Overall, 31 (16.4%) patients in the placebo+SoC group were admitted in the ICU compared to 39 (9.6%) patients in the anakinra+SoC group.

End point type	Secondary

End point timeframe:

90 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	39		
Units: days				
median (full range (min-max))	15 (1 to 39)	7.5 (2 to 19)		

Attachments (see zip file)	Time until discharge from the ICU at Day 90 /Time until

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

The univariate Cox regression analysis showed that the median time until ICU discharge was 7.5 days shorter in the anakinra+SoC group than in the placebo+SoC group (HR: 2.31; 95% CI: 1.08-4.93; p=0.031). A multivariate analysis was not possible for this endpoint due to the small number of

Comparison groups	Treatment Arm 1 v Treatment Arm 2

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.031 [14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	4.93

Notes:

[13] - Null hypothesis testing

[14] - p=0.031

Secondary: WHO-CPS at Day 60

End point title	WHO-CPS at Day 60

End point description:

End point type	Secondary

End point timeframe:

60 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	392		
Units: Individuals				
Fully recovered PCR(-)	93	280		
Asymptomatic PCR (+)	4	7		
Symptomatic independent	51	70		
Symptomatic assistance needed	9	10		
Hospitalized no need for oxygen	1	1		
Hospitalized with nasal/mask oxygen	4	1		
Need for HFO or NIV	0	0		
Mechanical ventilation with P/F >150	1	0		
Mechanical ventilation with P/F <150 or vasopresso	1	0		
Mechanical ventilation with P/F <150 and vasopress	1	2		
Dead	18	21		

Attachments (see zip file)	WHO-CPS by Day 60 /WHO-CPS by Day 60.tiff

Statistical analyses

Statistical analysis title	Ordinal logistic regression

Statistical analysis description:

Covariates entered in the multivariate model were those used for stratified randomization. The ordinal regression analysis showed that anakinra treatment reduced the odds for higher scores on the 11-point WHO-CPS at Day 60 compared to placebo (OR: 0.40, 95% CI: 0.28-0.58, p<0.0001).

Comparison groups	Treatment Arm 1 v Treatment Arm 2
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001 [16]
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.58

Notes:

[15] - Null hypothesis testing

[16] - p<0.0001

Secondary: WHO-CPS at Day 90

End point title	WHO-CPS at Day 90

End point description:

Covariates entered in the multivariate model were those used for stratified randomization. The ordinal regression analysis showed that anakinra treatment reduced the odds of higher scores on the 11-point WHO-CPS at Day 90 compared to placebo (OR: 0.50, 95% CI: 0.34-0.74, p=0.001).

End point type	Secondary

End point timeframe:

90 days

End point values	Treatment Arm 1	Treatment Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	388		
Units: Individuals				
Fully recovered PCR (-)	115	304		
Asymptomatic PCR (+)	2	2		
Symptomatic independent	34	50		
Symptomatic assistance needed	4	8		
Hospitalized no need for oxygen	3	1		
Hospitalized with nasal/mask oxygen	1	0		
Need for HFO or NIV	0	0		
Mechanical ventilation with P/F >150	1	1		
Mechanical ventilation with P/F <150 or vasopresso	0	0		
Mechanical ventilation with P/F <150 and vasopress	0	0		
Dead	19	22		

Attachments (see zip file)	WHO-CPS by Day 90 /WHO-CPS by Day 90.tiff

Statistical analyses

Statistical analysis title	Ordinal logistic regression

Statistical analysis description:

Covariates entered in the multivariate model were those used for stratified randomization. The ordinal regression analysis showed that anakinra treatment reduced the odds of higher scores on the 11-point WHO-CPS at Day 90 compared to placebo (OR: 0.50, 95% CI: 0.34-0.74, p=0.001).

Comparison groups	Treatment Arm 1 v Treatment Arm 2
Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.001 [18]
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.74

Notes:

[17] - Null hypothesis testing

[18] - p=0.001

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 23 December 2020-28 June 2021	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	Treatment Arm 1
Reporting group description: 0.67 mL of 0.9% sodium chloride, administered s.c. once daily for 10 days	
Reporting group title	Treatment Arm 2
Reporting group description: Anakinra 100 mg (0.67 mL) in a prefilled syringe, administered s.c. once daily for 10 days	

Serious adverse events	Treatment Arm 1	Treatment Arm 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 189 (21.69%)	65 / 405 (16.05%)	
number of deaths (all causes)	17	18	
number of deaths resulting from adverse events	17	18	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematoma muscle			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	4 / 189 (2.12%)	6 / 405 (1.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Hospitalization			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device related infection			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 189 (1.06%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumomediastinum			
subjects affected / exposed	2 / 189 (1.06%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumothorax			
subjects affected / exposed	2 / 189 (1.06%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pulmonary fibrosis			

subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltrasferase increased			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 189 (0.53%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	2 / 189 (1.06%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 189 (0.53%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 189 (0.53%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 189 (1.59%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 189 (0.00%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Mesenteritis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 189 (0.53%)	4 / 405 (0.99%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Abdominal infection			

subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacteremia			
subjects affected / exposed	5 / 189 (2.65%)	11 / 405 (2.72%)	
occurrences causally related to treatment / all	0 / 5	0 / 11	
deaths causally related to treatment / all	0 / 2	0 / 4	
Clostridioides difficile infection			
subjects affected / exposed	2 / 189 (1.06%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung empyema			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hospital-acquired infection			
subjects affected / exposed	7 / 189 (3.70%)	10 / 405 (2.47%)	
occurrences causally related to treatment / all	1 / 7	1 / 10	
deaths causally related to treatment / all	0 / 3	0 / 4	
Ventilator-associated pneumonia			
subjects affected / exposed	15 / 189 (7.94%)	9 / 405 (2.22%)	
occurrences causally related to treatment / all	2 / 15	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital-acquired pneumonia			
subjects affected / exposed	5 / 189 (2.65%)	6 / 405 (1.48%)	
occurrences causally related to treatment / all	1 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	4 / 189 (2.12%)	5 / 405 (1.23%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	5 / 189 (2.65%)	4 / 405 (0.99%)	
occurrences causally related to treatment / all	1 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 189 (0.53%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and skin structure infection			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 189 (1.06%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 189 (1.06%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 189 (0.53%)	4 / 405 (0.99%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 189 (0.53%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 189 (0.00%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment Arm 1	Treatment Arm 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 189 (82.54%)	335 / 405 (82.72%)	
Investigations			
Aminotransferase increase			
subjects affected / exposed	63 / 189 (33.33%)	145 / 405 (35.80%)	
occurrences (all)	63	145	
Amylase increase			
subjects affected / exposed	13 / 189 (6.88%)	19 / 405 (4.69%)	
occurrences (all)	13	19	
Vascular disorders			
Epistaxis			
subjects affected / exposed	2 / 189 (1.06%)	10 / 405 (2.47%)	
occurrences (all)	2	11	
Superficial thrombophlebitis			
subjects affected / exposed	3 / 189 (1.59%)	3 / 405 (0.74%)	
occurrences (all)	3	3	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	19 / 189 (10.05%)	36 / 405 (8.89%)	
occurrences (all)	20	36	
Arrythmia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 405 (0.25%)	
occurrences (all)	0	1	
Sinus tachycardia			

subjects affected / exposed	7 / 189 (3.70%)	16 / 405 (3.95%)	
occurrences (all)	7	16	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 189 (4.23%)	16 / 405 (3.95%)	
occurrences (all)	8	16	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	5 / 189 (2.65%)	14 / 405 (3.46%)	
occurrences (all)	5	14	
Leukocytosis			
subjects affected / exposed	19 / 189 (10.05%)	39 / 405 (9.63%)	
occurrences (all)	22	48	
Neutropenia			
subjects affected / exposed	1 / 189 (0.53%)	12 / 405 (2.96%)	
occurrences (all)	1	13	
Lymphocytopenia			
subjects affected / exposed	25 / 189 (13.23%)	40 / 405 (9.88%)	
occurrences (all)	29	47	
Anemia			
subjects affected / exposed	37 / 189 (19.58%)	59 / 405 (14.57%)	
occurrences (all)	39	61	
Thrombocytopenia			
subjects affected / exposed	4 / 189 (2.12%)	9 / 405 (2.22%)	
occurrences (all)	5	10	
Thrombocytosis			
subjects affected / exposed	13 / 189 (6.88%)	24 / 405 (5.93%)	
occurrences (all)	13	24	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 189 (0.00%)	2 / 405 (0.49%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Nausea, Vomiting			
subjects affected / exposed	1 / 189 (0.53%)	9 / 405 (2.22%)	
occurrences (all)	1	9	

Constipation			
subjects affected / exposed	16 / 189 (8.47%)	39 / 405 (9.63%)	
occurrences (all)	16	39	
Diarrhea			
subjects affected / exposed	8 / 189 (4.23%)	14 / 405 (3.46%)	
occurrences (all)	8	14	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 189 (1.59%)	15 / 405 (3.70%)	
occurrences (all)	3	15	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 189 (5.82%)	33 / 405 (8.15%)	
occurrences (all)	12	34	
Delirium			
subjects affected / exposed	2 / 189 (1.06%)	3 / 405 (0.74%)	
occurrences (all)	2	3	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 189 (4.76%)	17 / 405 (4.20%)	
occurrences (all)	9	17	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	76 / 189 (40.21%)	148 / 405 (36.54%)	
occurrences (all)	85	161	
Hypoglycemia			
subjects affected / exposed	15 / 189 (7.94%)	34 / 405 (8.40%)	
occurrences (all)	15	35	
Hyponatremia			
subjects affected / exposed	23 / 189 (12.17%)	32 / 405 (7.90%)	
occurrences (all)	23	33	
Hypernatremia			
subjects affected / exposed	17 / 189 (8.99%)	46 / 405 (11.36%)	
occurrences (all)	20	52	
Hypokalemia			
subjects affected / exposed	12 / 189 (6.35%)	11 / 405 (2.72%)	
occurrences (all)	12	11	

Hyperkalemia			
subjects affected / exposed	13 / 189 (6.88%)	36 / 405 (8.89%)	
occurrences (all)	13	38	
Hypercalcemia			
subjects affected / exposed	1 / 189 (0.53%)	4 / 405 (0.99%)	
occurrences (all)	1	4	
Hypocalcemia			
subjects affected / exposed	20 / 189 (10.58%)	32 / 405 (7.90%)	
occurrences (all)	20	33	
Hypermagnesemia			
subjects affected / exposed	1 / 189 (0.53%)	2 / 405 (0.49%)	
occurrences (all)	1	2	
Hypomagnesemia			
subjects affected / exposed	1 / 189 (0.53%)	3 / 405 (0.74%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/34480127