Clinical trial results:
A prospective, randomized, factorial design, interventional study to compare the safety and efficacy of combinations of blockade of interleukin-6 pathway and interleukin-1 pathway to best standard of care in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome.

Summary

EudraCT number	2020-001500-41
Trial protocol	BE
Global end of trial date	21 May 2021

Results information

Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022

Trial information

Trial identification

Sponsor protocol code	COV-AID

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04330638
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZ Gent
Sponsor organisation address	C. Heymanslaan 10, Ghent, Belgium, 9000
Public contact	HIRUZ CTU, University Hospital Ghent, +32 93320500, hiruz.ctu@uzgent.be
Scientific contact	HIRUZ CTU, University Hospital Ghent, +32 93320500, hiruz.ctu@uzgent.be

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	10 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2020
Global end of trial reached?	Yes
Global end of trial date	21 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study if blockade of IL-6 +/- IL-1 to block the cytokine storm and acute lung injury in comparison with usual care reduces time to clinical improvement as defined by an increase of more than 2 on the 6 point ordinal scale or discharge from the hospital

Protection of trial subjects:

Ethics review and approval, informed consent, supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 342
Worldwide total number of subjects	342
EEA total number of subjects	342

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)	167
From 65 to 84 years	166
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

342 patients were screened in the period from 04-apr-2020 till 06-dec-2020. 342 patients were included,
342 patients were randomised. End of trial notification
was dated 21-may-2021 (last patient last visit) and submitted to EC and CA 08-jul-2021.

Pre-assignment

Screening details:

Confirmed COVID-19 patients between the age of 18 and 80 years were screened for acute hypoxic respiratory failure (saturation <93% on minimal 2 L/min O2 or PaO2/FiO2 <350). Invasive mechanical ventilation >24h, history of severe allergic reactions and unlikely to servive beyond 48h were the most important exclusion criteria.

Period 1

Period 1 title	overall trial
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Usual Care

Arm description:

Usual Care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	B: Kineret

Arm description:

Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital)

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

Dosage and administration details:

Kineret® (Anakinra) 100mg pre-filled syringe.
Will be given 1x / day 100 mg SC 28 days (or until discharge from hospital)
Do not shake. Allow the pre-filled syringe to reach room temperature before the injection.
Subcutaneous injection; It is recommended that the injection site would be varied to avoid discomfort at the site of injection. Cooling the injection site, prewarming/preheating the injection liquid to reach room temperature, use of cold packs (before and after the injection) and use of topical glucocorticoids and antihistamines after injection may reduce the signs and symptoms of the reaction at the injection site.

Arm title	C: Sylvant

Arm description:

Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate.

Arm type	Experimental

Investigational medicinal product name	Sylvant
Investigational medicinal product code	
Other name	Siltuximab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sylvant® (Siltuximab) 100mg powder concentrate.
Single IV infusion at a dose of 11 mg / kg given over 1 hour as an intravenous infusion in glucose 5% (Ad-preparation: the same volume of product must be withdrawn from the infusion before adding the Sylvant®)
Administered via using PVC, or polyurethane (PU), or PE coated administration sets with a 0.2-micron in-line polyethersulfone (PES) filter.

Investigational medicinal product name	Sylvant
Investigational medicinal product code	
Other name	Siltuximab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sylvant® (Siltuximab) 400mg powder concentrate.
Single IV infusion at a dose of 11 mg / kg given over 1 hour as an intravenous infusion in glucose 5% (Ad-preparation: the same volume of product must be withdrawn from the infusion before adding the Sylvant®)
Administered via using PVC, or polyurethane (PU), or PE coated administration sets with a 0.2-micron in-line polyethersulfone (PES) filter.

Arm title	D: Kineret + Sylvant

Arm description:

Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital) +
Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400 mg powder concentrate.

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

Dosage and administration details:

Kineret® (Anakinra) 100mg pre-filled syringe.
Will be given 1x / day 100 mg SC 28 days (or until discharge from hospital)
Do not shake. Allow the pre-filled syringe to reach room temperature before the injection.
Subcutaneous injection; It is recommended that the injection site would be varied to avoid discomfort at the site of injection. Cooling the injection site, prewarming/preheating the injection liquid to reach room temperature, use of cold packs (before and after the injection) and use of topical glucocorticoids and antihistamines after injection may reduce the signs and symptoms of the reaction at the injection site.

Investigational medicinal product name	Sylvant
Investigational medicinal product code	
Other name	Siltuximab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sylvant® (Siltuximab) 100mg powder concentrate.
Single IV infusion at a dose of 11 mg / kg given over 1 hour as an intravenous infusion in glucose 5% (Ad-preparation: the same volume of product must be withdrawn from the infusion before adding the Sylvant®)
Administered via using PVC, or polyurethane (PU), or PE coated administration sets with a 0.2-micron in-line polyethersulfone (PES) filter.

Investigational medicinal product name	Sylvant
Investigational medicinal product code	
Other name	Siltuximab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sylvant® (Siltuximab) 400mg powder concentrate.
Single IV infusion at a dose of 11 mg / kg given over 1 hour as an intravenous infusion in glucose 5% (Ad-preparation: the same volume of product must be withdrawn from the infusion before adding the Sylvant®)
Administered via using PVC, or polyurethane (PU), or PE coated administration sets with a 0.2-micron in-line polyethersulfone (PES) filter.

Arm title	E: Roactemra

Arm description:

Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Arm type	Experimental
Investigational medicinal product name	Roactemra
Investigational medicinal product code	
Other name	Tocilizimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion).
Single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection 8mg / kg (= 0.4ml / kg) in an infusion of 100ml NaCl 0.9% and administration over 1 hour. No further specifications regarding the use of a 0.2 or 0.22 filter when administered.

Investigational medicinal product name	Roactemra
Investigational medicinal product code	
Other name	Tocilizimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Roactemra® (tocilizumab) IV infusion prepared from Prefilled syringe 162mg / 0.9ml SC.
Single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection 8mg / kg (= 0.4ml / kg) in an infusion of 100ml NaCl 0.9% and administration over 1 hour. Use a PO, PE, PP, PBD or PUR infusion line with 0.2 or 0.22 µm PES or PS filter during administation. As a measure of precaution, an inline filter is mandatory.

Arm title	F: Kineret + Roactemra

Arm description:

Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital) +
Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

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

Dosage and administration details:

Kineret® (Anakinra) 100mg pre-filled syringe.
Will be given 1x / day 100 mg SC 28 days (or until discharge from hospital)
Do not shake. Allow the pre-filled syringe to reach room temperature before the injection.
Subcutaneous injection; It is recommended that the injection site would be varied to avoid discomfort at the site of injection. Cooling the injection site, prewarming/preheating the injection liquid to reach room

temperature, use of cold packs (before and after the injection) and use of topical glucocorticoids and antihistamines after injection may reduce the signs and symptoms of the reaction at the injection site.

Investigational medicinal product name	Roactemra
Investigational medicinal product code	
Other name	Tocilizimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion).
single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection 8mg / kg (= 0.4ml / kg) in an infusion of 100ml NaCl 0.9% and administration over 1 hour. No further specifications regarding the use of a 0.2 or 0.22 filter when administered.

Investigational medicinal product name	Roactemra
Investigational medicinal product code	
Other name	Tocilizimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Roactemra® (tocilizumab) IV infusion prepared from Prefilled syringe 162mg / 0.9ml SC.
Single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection 8mg / kg (= 0.4ml / kg) in an infusion of 100ml NaCl 0.9% and administration over 1 hour. Use a PO, PE, PP, PBD or PUR infusion line with 0.2 or 0.22 µm PES or PS filter during administation. As a measure of precaution, an inline filter is mandatory.

Number of subjects in period 1	A: Usual Care	B: Kineret	C: Sylvant
Started	74	44	75
Completed	56	30	52
Not completed	18	14	23
Adverse event, serious fatal	9	10	15
Consent withdrawn by subject	4	-	-
unknown	2	2	5
Lost to follow-up	3	2	3

Number of subjects in period 1	D: Kineret + Sylvant	E: Roactemra	F: Kineret + Roactemra
Started	36	81	32
Completed	27	65	25
Not completed	9	16	7
Adverse event, serious fatal	6	10	5
Consent withdrawn by subject	-	-	-
unknown	1	3	2
Lost to follow-up	2	3	-

Period 2

Period 2 title	First 28 days
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	No IL-1 blockade

Arm description:

Some patients received IL-6 blockade with Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate, OR Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Arm type	Control group in the factorial design

No investigational medicinal product assigned in this arm

Arm title	IL-1 blockade

Arm description:

All patients received Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital).

Some patients also received Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate, OR
Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

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

Dosage and administration details:

Kineret® (Anakinra) 100mg pre-filled syringe.
Will be given 1x / day 100 mg SC 28 days (or until discharge from hospital)
Do not shake. Allow the pre-filled syringe to reach room temperature before the injection.
Subcutaneous injection; It is recommended that the injection site would be varied to avoid discomfort at the site of injection. Cooling the injection site, prewarming/preheating the injection liquid to reach room temperature, use of cold packs (before and after the injection) and use of topical glucocorticoids and antihistamines after injection may reduce the signs and symptoms of the reaction at the injection site.

Arm title	No IL-6 blockade

Arm description:

Some patients received Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital)

Arm type	Control group in the factorial design

No investigational medicinal product assigned in this arm

Arm title	IL-6 blockade

Arm description:

Patients received either Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate, OR Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Some patients also received Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital)

Arm type	Experimental

Investigational medicinal product name	Roactemra
Investigational medicinal product code	
Other name	Tocilizimab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion).
Single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection 8mg / kg (= 0.4ml / kg) in an infusion of 100ml NaCl 0.9% and administration over 1 hour. No further specifications regarding the use of a 0.2 or 0.22 filter when administered.

Investigational medicinal product name	Sylvant
Investigational medicinal product code	
Other name	Siltuximab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sylvant® (Siltuximab) 100mg powder concentrate.
Single IV infusion at a dose of 11 mg / kg given over 1 hour as an intravenous infusion in glucose 5% (Ad-preparation: the same volume of product must be withdrawn from the infusion before adding the Sylvant®)
Administered via using PVC, or polyurethane (PU), or PE coated administration sets with a 0.2-micron in-line polyethersulfone (PES) filter.

Number of subjects in period 2	No IL-1 blockade	IL-1 blockade	No IL-6 blockade
Started	230	112	115
Completed	200	95	99
Not completed	30	17	16
Adverse event, serious fatal	26	17	14
Consent withdrawn by subject	4	-	2

Number of subjects in period 2	IL-6 blockade
Started	227
Completed	196
Not completed	31
Adverse event, serious fatal	29
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	342	342	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	65		
inter-quartile range (Q1-Q3)	54 to 73	-	
Gender categorical Units: Subjects			
Female	77	77	
Male	265	265	
Ordinal scale			
6-point ordinal scale: 1 death, 2 on invasive mechanical ventilation or ECMO, 3 on non-invasive ventilation or high flow oxygen devices, 4 hospitalized, requiring supplemental oxygenn, 5 hospitalized, not requiring supplemental oxygen, 6 not hospitalized			
Units: Subjects			
2.	39	39	
3.	128	128	
4.	169	169	
5.	6	6	
Ethnicity Units: Subjects			
White	278	278	
Middle Eastern-Arabian	40	40	
Black	9	9	
Asian	7	7	
Other	8	8	
Glucocorticoids at day of randomisation Units: Subjects			
Yes	213	213	
No	129	129	

SOFA score			
Severity of organ failure assessment			
Units: N/A			
median	3		
inter-quartile range (Q1-Q3)	2 to 4	-	
PaO2/FiO2 ratio at baseline			
The ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2; PaO2/FiO2)			
Units: mmHg			
median	150		
inter-quartile range (Q1-Q3)	90 to 248	-	

End points reporting groups

Reporting group title	A: Usual Care

Reporting group description:

Usual Care

Reporting group title	B: Kineret

Reporting group description:

Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital)

Reporting group title	C: Sylvant

Reporting group description:

Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate.

Reporting group title	D: Kineret + Sylvant

Reporting group description:

Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital) +
Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400 mg powder concentrate.

Reporting group title	E: Roactemra

Reporting group description:

Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Reporting group title	F: Kineret + Roactemra

Reporting group description:

Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital) +
Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Reporting group title	No IL-1 blockade

Reporting group description:

Some patients received IL-6 blockade with Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate, OR Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Reporting group title	IL-1 blockade

Reporting group description:

All patients received Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital).

Some patients also received Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate, OR
Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Reporting group title	No IL-6 blockade

Reporting group description:

Some patients received Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days (or until discharge from hospital)

Reporting group title	IL-6 blockade

Reporting group description:

Patients received either Sylvant® (Siltuximab) single IV infusion from 100mg powder concentrate and 400mg powder concentrate, OR Roactemra® (tocilizumab) IV- Infusion prepared starting from flasks containing 400mg/20ml stock solution (to dilute for infusion) or from Prefilled syringe 162mg / 0.9ml SC

Some patients also received Kineret® (Anakinra) 100mg pre-filled syringe given 1x / day for 28 days

(or until discharge from hospital)

Primary: Time to clinical improvement	
End point title	Time to clinical improvement
End point description: Median time to clinical improvement	
End point type	Primary
End point timeframe: First 28 days	

End point values	No IL-1 blockade	IL-1 blockade	No IL-6 blockade	IL-6 blockade
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	230	112	115	227
Units: days	12	12	12	11

Statistical analyses

Statistical analysis title	Kaplan-Meier estimates for IL-1 blockade
Statistical analysis description: Kaplan-Meier estimates of the cumulative incidence function for clinical improvement with pointwise 95% confidence intervals according to the allocated treatment for the first randomization (IL-1 blockade vs. no IL-1 blockade).	
Comparison groups	No IL-1 blockade v IL-1 blockade
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.21

Statistical analysis title	Kaplan-Meier estimates for IL-6 blockade
Statistical analysis description: Kaplan-Meier estimates of the cumulative incidence function for clinical improvement with pointwise 95% confidence intervals according to the allocated treatment for the second randomization (IL-6 blockade vs. no IL-6 blockade).	
Comparison groups	No IL-6 blockade v IL-6 blockade

Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.29

Primary: Efficacy endpoint for IL-6 blockade

End point title	Efficacy endpoint for IL-6 blockade

End point description:

Median time to clinical improvement. Clinical improvement was defined as an increase of 2 points on the 6-point ordinal scale or discharge.

End point type	Primary

End point timeframe:

First 28 days

End point values	No IL-6 blockade	IL-6 blockade		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	227		
Units: days	12	11		

Statistical analyses

Statistical analysis title	Estimated probability of clinical improvement

Statistical analysis description:

Estimated probability of having experienced clinical improvement at day 28.

Comparison groups	No IL-6 blockade v IL-6 blockade
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.29

Adverse events

Adverse events information	
Timeframe for reporting adverse events: screening until follow-up	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0
Reporting groups	
Reporting group title	A: Usual Care
Reporting group description: -	
Reporting group title	B: Kineret
Reporting group description: -	
Reporting group title	C: Sylvant
Reporting group description: -	
Reporting group title	D: Kineret + Sylvant
Reporting group description: -	
Reporting group title	E: Roactemra
Reporting group description: -	
Reporting group title	F: Kineret + Roactemra
Reporting group description: -	

Serious adverse events	A: Usual Care	B: Kineret	C: Sylvant
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 74 (18.92%)	12 / 44 (27.27%)	21 / 75 (28.00%)
number of deaths (all causes)	9	10	15
number of deaths resulting from adverse events			
Vascular disorders			
Arterial thromboembolism			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (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
Thromboembolic event			
subjects affected / exposed	1 / 74 (1.35%)	1 / 44 (2.27%)	0 / 75 (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
Surgical and medical procedures			
Other			

subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multi-organ failure			
subjects affected / exposed	3 / 74 (4.05%)	2 / 44 (4.55%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 0
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 74 (2.70%)	1 / 44 (2.27%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 1	1 / 2
Aspiration			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea			

subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Hypoxia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (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
Laryngeal stenosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (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
Pneumonitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Pneumothorax			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	2 / 74 (2.70%)	5 / 44 (11.36%)	9 / 75 (12.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 9
deaths causally related to treatment / all	0 / 2	0 / 5	0 / 7
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (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
Injury, poisoning and procedural complications			
postoperative haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Asystole			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 74 (0.00%)	1 / 44 (2.27%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Other			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve disease			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Nervous system disorders			
Edema cerebral			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Hydrocephalus			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Intracranial haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	1 / 44 (2.27%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Stroke			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Other			
subjects affected / exposed	0 / 74 (0.00%)	1 / 44 (2.27%)	0 / 75 (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
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	1 / 44 (2.27%)	0 / 75 (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
Jejunal haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 44 (2.27%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 74 (1.35%)	1 / 44 (2.27%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (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
Infections and infestations			
Hepatic infection			

subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 44 (2.27%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 74 (4.05%)	5 / 44 (11.36%)	6 / 75 (8.00%)
occurrences causally related to treatment / all	0 / 3	1 / 5	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 3
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (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

Serious adverse events	D: Kineret + Sylvant	E: Roactemra	F: Kineret + Roactemra
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 36 (22.22%)	15 / 81 (18.52%)	9 / 32 (28.13%)
number of deaths (all causes)	6	10	5
number of deaths resulting from adverse events			
Vascular disorders			
Arterial thromboembolism			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	0 / 32 (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
Thromboembolic event			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Surgical and medical procedures			
Other			

subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (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
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Multi-organ failure			
subjects affected / exposed	0 / 36 (0.00%)	2 / 81 (2.47%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	0 / 32 (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
Aspiration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Dyspnea			

subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Hypoxia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	0 / 32 (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
Laryngeal stenosis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Pneumothorax			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 36 (5.56%)	6 / 81 (7.41%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	2 / 2	0 / 6	0 / 1
deaths causally related to treatment / all	2 / 2	0 / 5	0 / 1
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
postoperative haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (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			
Asystole			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (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
Other			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Mitral valve disease			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Edema cerebral			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Hydrocephalus			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Intracranial haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Stroke			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Blood and lymphatic system disorders			
Other			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (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
Jejunal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hepatic infection			

subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	3 / 36 (8.33%)	2 / 81 (2.47%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	3 / 3	1 / 2	2 / 2
deaths causally related to treatment / all	2 / 2	1 / 2	1 / 1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	0 / 32 (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	A: Usual Care	B: Kineret	C: Sylvant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 74 (50.00%)	25 / 44 (56.82%)	45 / 75 (60.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 74 (4.05%)	3 / 44 (6.82%)	7 / 75 (9.33%)
occurrences (all)	4	3	10
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 74 (4.05%)	2 / 44 (4.55%)	5 / 75 (6.67%)
occurrences (all)	6	2	8
creatinine increased			
subjects affected / exposed	2 / 74 (2.70%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences (all)	2	0	1
GGT inncreased			

subjects affected / exposed	2 / 74 (2.70%)	2 / 44 (4.55%)	5 / 75 (6.67%)
occurrences (all)	4	3	6
Neutrophil count decreased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	4 / 75 (5.33%)
occurrences (all)	0	0	12
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 74 (5.41%)	3 / 44 (6.82%)	4 / 75 (5.33%)
occurrences (all)	4	3	4
Hypotension			
subjects affected / exposed	4 / 74 (5.41%)	3 / 44 (6.82%)	1 / 75 (1.33%)
occurrences (all)	4	3	1
Thromboembolic event			
subjects affected / exposed	1 / 74 (1.35%)	3 / 44 (6.82%)	4 / 75 (5.33%)
occurrences (all)	1	3	5
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 74 (4.05%)	0 / 44 (0.00%)	7 / 75 (9.33%)
occurrences (all)	3	0	7
Sinus bradycardia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 44 (0.00%)	8 / 75 (10.67%)
occurrences (all)	1	0	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 74 (4.05%)	3 / 44 (6.82%)	4 / 75 (5.33%)
occurrences (all)	3	3	8
Other			
subjects affected / exposed	0 / 74 (0.00%)	3 / 44 (6.82%)	4 / 75 (5.33%)
occurrences (all)	0	3	5
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 74 (13.51%)	5 / 44 (11.36%)	9 / 75 (12.00%)
occurrences (all)	11	5	10
Diarrhoea			

subjects affected / exposed	2 / 74 (2.70%)	3 / 44 (6.82%)	3 / 75 (4.00%)
occurrences (all)	3	4	3
gastroparesis			
subjects affected / exposed	3 / 74 (4.05%)	3 / 44 (6.82%)	1 / 75 (1.33%)
occurrences (all)	3	3	1
Nausea			
subjects affected / exposed	4 / 74 (5.41%)	0 / 44 (0.00%)	2 / 75 (2.67%)
occurrences (all)	4	0	3
Vomiting			
subjects affected / exposed	0 / 74 (0.00%)	1 / 44 (2.27%)	1 / 75 (1.33%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	1 / 74 (1.35%)	1 / 44 (2.27%)	0 / 75 (0.00%)
occurrences (all)	1	1	0
Other			
subjects affected / exposed	0 / 74 (0.00%)	5 / 44 (11.36%)	2 / 75 (2.67%)
occurrences (all)	0	6	2
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Delirium			
subjects affected / exposed	3 / 74 (4.05%)	2 / 44 (4.55%)	4 / 75 (5.33%)
occurrences (all)	3	2	4
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 74 (2.70%)	3 / 44 (6.82%)	2 / 75 (2.67%)
occurrences (all)	2	3	2
other			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis	Additional description: lower limb		

subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 74 (2.70%)	2 / 44 (4.55%)	2 / 75 (2.67%)
occurrences (all)	2	2	3
lung infection			
subjects affected / exposed	7 / 74 (9.46%)	4 / 44 (9.09%)	8 / 75 (10.67%)
occurrences (all)	13	5	17
Sepsis			
subjects affected / exposed	3 / 74 (4.05%)	0 / 44 (0.00%)	5 / 75 (6.67%)
occurrences (all)	3	0	5
Urinary tract infection			
subjects affected / exposed	4 / 74 (5.41%)	1 / 44 (2.27%)	1 / 75 (1.33%)
occurrences (all)	4	1	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 44 (0.00%)	4 / 75 (5.33%)
occurrences (all)	2	0	4
Hyperkalaemia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 44 (4.55%)	4 / 75 (5.33%)
occurrences (all)	0	2	4
Hypertriglyceridaemia			
subjects affected / exposed	1 / 74 (1.35%)	2 / 44 (4.55%)	3 / 75 (4.00%)
occurrences (all)	1	2	3
Hypokalaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 44 (0.00%)	4 / 75 (5.33%)
occurrences (all)	0	0	4
other			
subjects affected / exposed	2 / 74 (2.70%)	1 / 44 (2.27%)	5 / 75 (6.67%)
occurrences (all)	3	1	5

Non-serious adverse events	D: Kineret + Sylvant	E: Roactemra	F: Kineret + Roactemra
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 36 (47.22%)	35 / 81 (43.21%)	17 / 32 (53.13%)
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 36 (8.33%)	7 / 81 (8.64%)	1 / 32 (3.13%)
occurrences (all)	3	11	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 36 (5.56%)	5 / 81 (6.17%)	0 / 32 (0.00%)
occurrences (all)	2	7	0
creatinine increased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
GGT inncreased			
subjects affected / exposed	0 / 36 (0.00%)	2 / 81 (2.47%)	0 / 32 (0.00%)
occurrences (all)	0	4	0
Neutrophil count decreased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Platelet count decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 36 (2.78%)	3 / 81 (3.70%)	3 / 32 (9.38%)
occurrences (all)	1	3	3
Hypotension			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Thromboembolic event			
subjects affected / exposed	0 / 36 (0.00%)	3 / 81 (3.70%)	0 / 32 (0.00%)
occurrences (all)	0	6	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	3 / 32 (9.38%)
occurrences (all)	1	0	3
Sinus bradycardia			
subjects affected / exposed	2 / 36 (5.56%)	2 / 81 (2.47%)	0 / 32 (0.00%)
occurrences (all)	2	2	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 36 (8.33%)	2 / 81 (2.47%)	0 / 32 (0.00%)
occurrences (all)	3	2	0
Other			
subjects affected / exposed	4 / 36 (11.11%)	3 / 81 (3.70%)	0 / 32 (0.00%)
occurrences (all)	4	3	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 36 (11.11%)	8 / 81 (9.88%)	7 / 32 (21.88%)
occurrences (all)	4	8	7
Diarrhoea			
subjects affected / exposed	1 / 36 (2.78%)	2 / 81 (2.47%)	1 / 32 (3.13%)
occurrences (all)	1	2	1
gastroparesis			
subjects affected / exposed	0 / 36 (0.00%)	3 / 81 (3.70%)	1 / 32 (3.13%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	2 / 36 (5.56%)	0 / 81 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Vomiting			
subjects affected / exposed	2 / 36 (5.56%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	1 / 36 (2.78%)	1 / 81 (1.23%)	2 / 32 (6.25%)
occurrences (all)	1	1	2
Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 36 (0.00%)	2 / 81 (2.47%)	1 / 32 (3.13%)
occurrences (all)	0	2	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 36 (0.00%)	1 / 81 (1.23%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
other			
subjects affected / exposed	2 / 36 (5.56%)	1 / 81 (1.23%)	0 / 32 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis	Additional description: lower limb		
subjects affected / exposed	2 / 36 (5.56%)	0 / 81 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
lung infection			
subjects affected / exposed	3 / 36 (8.33%)	8 / 81 (9.88%)	5 / 32 (15.63%)
occurrences (all)	5	10	7
Sepsis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 81 (2.47%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 81 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 36 (2.78%)	2 / 81 (2.47%)	3 / 32 (9.38%)
occurrences (all)	1	2	3
Hyperkalaemia			
subjects affected / exposed	0 / 36 (0.00%)	3 / 81 (3.70%)	0 / 32 (0.00%)
occurrences (all)	0	3	0
Hypertriglyceridaemia			
subjects affected / exposed	2 / 36 (5.56%)	1 / 81 (1.23%)	3 / 32 (9.38%)
occurrences (all)	2	1	3

Hypokalaemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
other			
subjects affected / exposed	1 / 36 (2.78%)	0 / 81 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2020	Section 5.1 : Recent (≤14 days of) of flu-like symptoms or malaise prior to randomization) infection with COVID-19 -> changed to ≤16 days section 5.2 : frailty score. exclusion criteria: clinical frailty score >2 -> changed to clinical frailty score > 3 Section 5.1 , inclusion criteria: clinical frailty score deleted section 5.1 : COVID-19 diagnosis: serology and emerging technologies added as diagnostic test Section 5.1 : COVID-19 diagnosis Probable COVID-19 infection defined by chest CT-scan and clinical criteria added
09 April 2020	Addition Jessa Hospital Hasselt
21 April 2020	Addition of o CHR de la Citadelle o CHU Tivoli o Cliniques Saint-Pierre Ottignies o AZ Delta o AZ Sint-Lucas Gent o ZNA Section 5.1 : IC1 Confident COVID diagnosis … Section 5.1: IC 4 clarification FiO2 Section 5.1: added extra IC Female subject need to use adequate contraception during treatment and 3 months after treatment Section 7.1.3 : Roactemra sc to IV clarification Section 8.4 : schematic overview Procalcitonin explicit added in overview Section 12.6 data safety monitoring board will be foreseen Section 7.1.3 Dose justification added
18 June 2020	Section 3.2: ARDS definition changed to "adjusted Berlin criteria". Section 5.1: typo corrected Section 5.2: Clarification Frailty score added: clinical frailty scale above 3 (This frailty score is the patient status before first symptoms of COVID-19 episode.) Section 5.2: Exclusion criteria added: Patient on ECMO at time of screening Section 7.1.4: Dose adjustment permitted for KINERET if kidney function falls below 30ml/min GFR. Dosing to be adjusted to 100 mg once every other day (q2d) Section 8.4: lay-out of flowchart simplified. Assessments removed: - Clinical Sign Score and NEWS2 - HScore only at D1 - Daily anamnesis and physical examination not requested anymore, only per standard of care or on clinical grounds. - Arterial Blood Gas only required at D0/1, D6, D15 or discharge whichever comes first - Laboratory assessments: ESR, ureum, troponins, CK removed. Procalcitonine required at least 3x/week. Section 9.3: 1500 RPM or 410 g adjusted to -> 1770g Section 12.3: Contact details Marketing Authorisation Holder, SOBI, ROCHE, EUSAPHARMA: removed Section 12.4: Study team informs company that provides IMP was erased

10 November 2020	Section 8.4: schematic overview error corrected and column "Discharge (only if after D15)" removed. Section 3.2: PEEP > 5 cm H20 on invasive or non-invasive ventilation or flow ≥ 50L/min on HFOT (Optiflow) (Typo "≥ 60L/min" corrected to "≥ 50L/min.) Section 8.2 and section 8.4: If an arterial blood gas value is available of less than 24 hours before randomization, there's no need to have a new ABG done on Day 0/1. Section 8.4: time window of assessment of vital signs (6-10 AM) is not applicable for the follow-up visit. Section 7.1.4 : In case kidney function falls below 30ml/min GFR, dosing of KINERET® needs to be adjusted to 100mg every other day (q2d). section 7.1.3: Sylvant® (Siltuximab) 100mg powder concentrate added Section 2: Secondary objectives are refined Section 3: Secondary endpoints are refined into sensitivity endpoints for the primary endpoints, secondary endpoints and related sensitivity endpoints, exploratory endpoints, descriptive endpoints and safety endpoints. The description of the endpoints was clarified without substantive changes. Section 10.1 on the sample size calculation Section 10.2 on type of statistical methods clarifies Cox Proportional Hazards models will be stratified according to the other randomization and according to dexamethasone use (as usual care in the treatment of covid19 has changed). Models will not be stratified for centre. Section 10.2 on type of statistical methods Section 2.4 on the primary objective Section 2.6 on exploratory objectives Section 3 on endpoints Section 4.2.1 on the end of study duration for an individual subject Section 3.2: A new sensitivity endpoint related to the primary endpoint has been added Section 4.2 on end of study definition Section 10.1 on sample size calculation Section 3.3 on secondary endpoints Section 10.2 on type of statistical methods Section 3.6 on safety endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34756178