Clinical trial results:
A prospective, randomized, open-label, interventional study to investigate the efficacy of sargramostim (Leukine®) in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure.

Summary

EudraCT number	2020-001254-22
Trial protocol	BE
Global end of trial date	03 August 2021

Results information

Result version number	v1
This version publication date	13 March 2022
First version publication date	13 March 2022

Trial information

Trial identification

Sponsor protocol code	SARPAC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04326920
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	Cormaal Hetmanslaan 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	28 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2021
Global end of trial reached?	Yes
Global end of trial date	03 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate whether the administration of inhaled sargramostim (Leukine®) at a dose of 250 mcg daily during 5 days improves oxygenation in COVID-19 patients with acute hypoxic respiratory failure .

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	23 March 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research, Safety
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: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	55
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

87 patients were screened in the period from 25-mar-2020 till 29-sep-2020. 87 patients were included, 81 patients were randomised. 73 patients were included and completed the trial. End of trial notification was dated 26-feb-2021 (last patient last visit) and submitted to EC and CA 03-aug-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). Mechanical ventilation, high dose systemic corticosteroids, active myeloid malignancy and lithium carbonate therapy were the most important exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	usual care + sargramostim

Arm description:

usual care +
Sargramostim/Leukine® 125 mcg BID via inhalation, for 5 days (Group A)
Sargramostim/Leukine® 125 mcg/m2 once daily IV upon progression, for 5 days (Group C)

Arm type	Experimental
Investigational medicinal product name	sargramostim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Powder for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

LEUKINE® (sargramostim) prepared and administered for inhalation using nebulizer
LEUKINE for injection is a sterile, preservative-free lyophilized powder that requires reconstitution with 2mL normal saline solution. Once reconstituted, LEUKINE can be inhaled as an aqueous aerosol using either a vibrating mesh nebulizer (Philips InnospireGo) or jet nebulizer, per manufacturer instructions. (Nebulizers studied include: AKITA2 Apixneb, PARI LC-Plus set, PulmoAide, Pan LC, Aeroneb Solo Device). Use reconstituted LEUKINE® solution for inhalation within 16 hours following reconstitution and/or dilution.
Nebulizing is preferably done in an isolation negative pressure chamber, and if not, personnel should use an FFP2 mask. Patient should self-administer the medication and where possible, the room should not be entered within one hour after administration.

LEUKINE® (sargramostim) prepared and administered intravenously
For patients that are on a mechanical ventilator and cannot be treated

Arm title	usual care

Arm description:

Usual care +
Sargramostim/Leukine® 125 mcg/m2 once daily IV upon progression, for 5 days (Group D)

Arm type	Experimental

Investigational medicinal product name	sagramostim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

LEUKINE® (sargramostim) prepared and administered for inhalation using nebulizer
LEUKINE for injection is a sterile, preservative-free lyophilized powder that requires reconstitution with 2mL normal saline solution. Once reconstituted, LEUKINE can be inhaled as an aqueous aerosol using either a vibrating mesh nebulizer (Philips InnospireGo) or jet nebulizer, per manufacturer instructions. (Nebulizers studied include: AKITA2 Apixneb, PARI LC-Plus set, PulmoAide, Pan LC, Aeroneb Solo Device). Use reconstituted LEUKINE® solution for inhalation within 16 hours following reconstitution and/or dilution.
Nebulizing is preferably done in an isolation negative pressure chamber, and if not, personnel should use an FFP2 mask. Patient should self-administer the medication and where possible, the room should not be entered within one hour after administration.

LEUKINE® (sargramostim) prepared and administered intravenously
For patients that are on a mechanical ventilator and cannot be treated

Number of subjects in period 1	usual care + sargramostim	usual care
Started	40	41
Completed	40	39
Not completed	0	2
Consent withdrawn by subject	-	1
Consent withdrawn by physician	-	1

Baseline characteristics

Reporting groups	
Reporting group title	usual care + sargramostim
Reporting group description:	
usual care + Sargramostim/Leukine® 125 mcg BID via inhalation, for 5 days (Group A) Sargramostim/Leukine® 125 mcg/m2 once daily IV upon progression, for 5 days (Group C)	

Reporting group title	usual care
Reporting group description:	
Usual care + Sargramostim/Leukine® 125 mcg/m2 once daily IV upon progression, for 5 days (Group D)	

Reporting group values	usual care + sargramostim	usual care	Total
Number of subjects	40	41	81
Age categorical			
age 18-80			
Units: Subjects			
Adults (18-64 years)	29	26	55
From 65-84 years	11	15	26
Age continuous			
Units: years			
median	59	60	
inter-quartile range (Q1-Q3)	46 to 68	53 to 69	-
Gender categorical			
Units: Subjects			
Female	14	16	30
Male	26	25	51
Ethnicity			
Units: Subjects			
White	34	39	73
Black	4	0	4
Arabian	2	2	4
Comorbidity			
Units: Subjects			
Arterial hypertension	7	7	14
Diabetes mellitus	9	7	16
Cardiovascular disease	0	1	1
Chronic kidney disease	0	1	1
Severe liver disease	0	0	0
Chronic lung disease	0	0	0
Cancer	2	2	4
Patients witjout reported comorbidities	22	23	45
Smoking status			
Units: Subjects			
Current	0	3	3
Former	18	16	34
Never	22	22	44

Concommitant medication at randomization Units: Subjects			
Glucocorticoids	11	9	20
Antiviral drugs (remdesivir)	3	0	3
Hydroxychloroquine	24	26	50
Antibiotics	1	2	3
Patients without reported concommitant medication	1	4	5
6-category ordinal scale Units: Subjects			
5 Hospitalized, no supplemental oxygen	1	3	4
4 Hospitalized, supplemental oxygen	38	33	71
3 Hopsitalized, NIMV or HFOD	1	5	6
Lab values - C-reactive protein Units: mg/L			
median	73.2	83	
inter-quartile range (Q1-Q3)	39.1 to 122.8	38.4 to 180	-
Biomarkers in serum - IL1RA Units: ng/mL			
median	839.3	1288	
inter-quartile range (Q1-Q3)	595.8 to 1494	905.1 to 2350	-
Oxygenation - PaO2/FiO2 ratio Units: mmHg			
median	291.5	297	
inter-quartile range (Q1-Q3)	251.5 to 329	242 to 319.5	-
Oxygenation - P(A-a)O2 gradient Units: mmHg			
median	50.15	45.55	
inter-quartile range (Q1-Q3)	39.8 to 63.75	38.6 to 61.75	-
Lab values - eosinophil count Units: x 10^9/L			
median	0.01	0.02	
inter-quartile range (Q1-Q3)	0 to 0.1	0 to 0.09	-
Lab values - lymphocyte count Units: x 10^9/L			
median	1.08	0.88	
inter-quartile range (Q1-Q3)	0.83 to 1.4	0.65 to 1.22	-
Lab values - ferritin Units: mcg/L			
median	736.5	721	
inter-quartile range (Q1-Q3)	446.5 to 1063.5	425 to 1068	-
Lab values - D-dimer Units: nmol/L			
median	4.36	3.61	
inter-quartile range (Q1-Q3)	3.12 to 5.8	2.39 to 5.04	-
Lab values - lactate dehydrogenase Units: ukat/L			
median	4.98	5.98	
inter-quartile range (Q1-Q3)	4.14 to 6.4	4.31 to 6.86	-
Lab values - aspartate aminotransferase			

Units: ukat/L			
median	0.62	0.65	
inter-quartile range (Q1-Q3)	0.44 to 1.01	0.57 to 0.89	-
Lab values - alanine aminotransferase			
Units: ukat/L			
median	0.59	0.57	
inter-quartile range (Q1-Q3)	0.38 to 0.86	0.4 to 0.92	-
Lab values - creatinine			
Units: micromol/L			
median	75.14	78.68	
inter-quartile range (Q1-Q3)	68.07 to 88.4	68.07 to 92.82	-
Biomarkers in serum - IL-6			
Units: pg/mL			
median	11.54	11.54	
inter-quartile range (Q1-Q3)	4.85 to 36.84	4.85 to 36.84	-
Biomarkers in serum - IL-8			
Units: pg/mL			
median	22.51	27.44	
inter-quartile range (Q1-Q3)	14.14 to 32.11	15.91 to 46.49	-
Biomarkers in serum - IL-18			
Units: pg/mL			
median	101.3	150.7	
inter-quartile range (Q1-Q3)	73.8 to 164.7	87.13 to 198.3	-
Biomarkers in serum - C5a			
Units: ng/mL			
median	11.18	8.83	
inter-quartile range (Q1-Q3)	3.91 to 16.28	4.52 to 16.06	-
Biomarkers in serum - GM-CSF			
Units: fg/mL			
median	9.13	9.12	
inter-quartile range (Q1-Q3)	7.35 to 12.42	6.82 to 13.39	-
Biomarkers in serum - TNF			
Units: pg/mL			
median	16.32	14.77	
inter-quartile range (Q1-Q3)	12.17 to 20.13	8.53 to 25.91	-
BMI			
Units: kg/m^2			
median	28.6	27.6	
inter-quartile range (Q1-Q3)	26 to 33.8	24.7 to 33.1	-
Days since symptom onset			
Units: day			
median	11	10	
inter-quartile range (Q1-Q3)	8.5 to 14	9 to 13	-
Days since hospitalization			
Units: day			
median	3	3	
inter-quartile range (Q1-Q3)	2.5 to 4.5	3 to 5	-

Subject analysis sets

Subject analysis set title	modified intent-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Modified intent-to-treat population includes all patients who were randomized and received at least one dose of sargramostim and/or standard of care based on the treatment assigned at randomization.

Reporting group values	modified intent-to-treat		
Number of subjects	81		
Age categorical			
age 18-80			
Units: Subjects			
Adults (18-64 years)	55		
From 65-84 years	26		
Age continuous			
Units: years			
median	60		
inter-quartile range (Q1-Q3)	49 to 69		
Gender categorical			
Units: Subjects			
Female	30		
Male	51		
Ethnicity			
Units: Subjects			
White	73		
Black	4		
Arabian	4		
Comorbidity			
Units: Subjects			
Arterial hypertension	14		
Diabetes mellitus	16		
Cardiovascular disease	1		
Chronic kidney disease	1		
Severe liver disease	0		
Chronic lung disease	0		
Cancer	4		
Patients witjout reported comorbidities	45		
Smoking status			
Units: Subjects			
Current	3		
Former	34		
Never	44		
Concommitant medication at randomization			
Units: Subjects			
Glucocorticoids	20		
Antiviral drugs (remdesivir)	3		
Hydroxychloroquine	50		
Antibiotics	3		
Patients without reported concommitant medication	5		
6-category ordinal scale			
Units: Subjects			

5 Hospitalized, no supplemental oxygen	4		
4 Hospitalized, supplemental oxygen	71		
3 Hopsitalized, NIMV or HFOD	6		
Lab values - C-reactive protein			
Units: mg/L			
median	74.5		
inter-quartile range (Q1-Q3)	38.75 to 147.45		
Biomarkers in serum - IL1RA			
Units: ng/mL			
median	1162		
inter-quartile range (Q1-Q3)	678.4 to 1806		
Oxygenation - PaO2/FiO2 ratio			
Units: mmHg			
median			
inter-quartile range (Q1-Q3)			
Oxygenation - P(A-a)O2 gradient			
Units: mmHg			
median			
inter-quartile range (Q1-Q3)			
Lab values - eosinophil count			
Units: x 10^9/L			
median	0.02		
inter-quartile range (Q1-Q3)	0 to 0.1		
Lab values - lymphocyte count			
Units: x 10^9/L			
median	1		
inter-quartile range (Q1-Q3)	0.7 to 1.3		
Lab values - ferritin			
Units: mcg/L			
median	721		
inter-quartile range (Q1-Q3)	425 to 1068		
Lab values - D-dimer			
Units: nmol/L			
median	3.81		
inter-quartile range (Q1-Q3)	2.79 to 5.31		
Lab values - lactate dehydrogenase			
Units: ukat/L			
median	5.26		
inter-quartile range (Q1-Q3)	4.21 to 6.68		
Lab values - aspartate aminotransferase			
Units: ukat/L			
median	0.65		
inter-quartile range (Q1-Q3)	0.48 to 0.95		
Lab values - alanine aminotransferase			
Units: ukat/L			
median	0.58		
inter-quartile range (Q1-Q3)	0.4 to 0.89		
Lab values - creatinine			
Units: micromol/L			
median	77.35		

inter-quartile range (Q1-Q3)	68.07 to 92.82		
Biomarkers in serum - IL-6 Units: pg/mL			
median	11.54		
inter-quartile range (Q1-Q3)	4.85 to 24.9		
Biomarkers in serum - IL-8 Units: pg/mL			
median	23.99		
inter-quartile range (Q1-Q3)	15.91 to 39.73		
Biomarkers in serum - IL-18 Units: pg/mL			
median	131		
inter-quartile range (Q1-Q3)	80.32 to 184.8		
Biomarkers in serum - C5a Units: ng/mL			
median	9.94		
inter-quartile range (Q1-Q3)	4.37 to 16.12		
Biomarkers in serum - GM-CSF Units: fg/mL			
median	9.12		
inter-quartile range (Q1-Q3)	7.05 to 12.71		
Biomarkers in serum - TNF Units: pg/mL			
median	14.99		
inter-quartile range (Q1-Q3)	10.66 to 22.28		
BMI Units: kg/m^2			
median	28		
inter-quartile range (Q1-Q3)	25 to 33.4		
Days since symptom onset Units: day			
median	11		
inter-quartile range (Q1-Q3)	9 to 13		
Days since hospitalization Units: day			
median	3		
inter-quartile range (Q1-Q3)	3 to 5		

End points

End points reporting groups

Reporting group title	usual care + sargramostim

Reporting group description:

usual care +
Sargramostim/Leukine® 125 mcg BID via inhalation, for 5 days (Group A)
Sargramostim/Leukine® 125 mcg/m2 once daily IV upon progression, for 5 days (Group C)

Reporting group title	usual care

Reporting group description:

Usual care +
Sargramostim/Leukine® 125 mcg/m2 once daily IV upon progression, for 5 days (Group D)

Subject analysis set title	modified intent-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Modified intent-to-treat population includes all patients who were randomized and received at least one dose of sargramostim and/or standard of care based on the treatment assigned at randomization.

Primary: oxygenation parameters

End point title	oxygenation parameters

End point description:

The primary objective is to investigate whether the administration of inhaled sargramostim (Leukine®) at a dose of 250 mcg daily during 5 days improves oxygenation in COVID-19 patients with acute hypoxic respiratory failure.

End point type	Primary

End point timeframe:

D1-D6

End point values	usual care + sargramostim	usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: mmHg				
number (not applicable)	40	41		

Attachments (see zip file)	figure primary endpoint.jpg

Statistical analyses

Statistical analysis title	T test
Comparison groups	usual care + sargramostim v usual care

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: screening untill follow up	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	usual care + sargramostim
Reporting group description: -	
Reporting group title	usual care
Reporting group description: -	

Serious adverse events	usual care + sargramostim	usual care	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 40 (15.00%)	6 / 41 (14.63%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events	1	4	
Vascular disorders			
Thromboembolic event	Additional description: Pulmonary embolism		
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope	Additional description: Progressive symptomatic orthostatism with presyncope		
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Respiratory deterioration			

subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventilator associated pneumonia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory deterioration due to underlying MPO-ANCA vasculitis and aspergillosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia	Additional description: Increasing hypoxemia due to COVID-19		
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Persistent catatonic state and neurological deficits	Additional description: therefore abstinence from further therapy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Invasive aspergillosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multi-bacterial bacteremia causing hemorrhagic shock			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	usual care + sargramostim	usual care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 40 (60.00%)	20 / 41 (48.78%)	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	2 / 40 (5.00%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 40 (7.50%)	6 / 41 (14.63%)	
occurrences (all)	3	6	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 8	2 / 41 (4.88%) 2	
Hepatobiliary disorders Abnormal liver function subjects affected / exposed occurrences (all)	 1 / 40 (2.50%) 1	 0 / 41 (0.00%) 0	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2	 0 / 41 (0.00%) 0	
Infections and infestations Infectious disorder (not COVID-19) subjects affected / exposed occurrences (all)	 7 / 40 (17.50%) 7	 9 / 41 (21.95%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2020	correction includion criteria to PaO2/FiO2 below 350
17 April 2020	Section 6.1: Inclusion criteria 1 removed and changed to COVID-19 diagnosis confirmed by antigen detection test and/or PCR and/or positive serology, or any emerging and validated diagnostic laboratory test for COVID-19 within this period. Section 1.5, 6.1: Extra Inclusion criteria: In some patients, it may be impossible to get a confident laboratory confirmation of COVID-19 diagnosis after 24h of hospital admission because viral load is low and/or problems with diagnostic sensitivity. In those cases, in absence of an alternative diagnosis, and with highly suspect bilateral ground glass opacities on recent (<24h) chest-CT scan (confirmed by a radiologist and pulmonary physician as probable COVID-19), a patient can be enrolled as probable COVID-19 infected. In all cases, this needs confirmation by later seroconversion Section 10: redefining sampling.due to addition of extra study sites. Section 8.1.5: better definition of duration of treatment Section 13.6: Despite the known safety profile of the study medications and study design, a DSMB is foreseen. General: Better definition of progressive disease: Progression to ARDS requiring mechanical ventilation is removed and replaced by: progressive disease requiring mechanical ventilatory support. General: Safety follow-up period is 10-20 weeks. Section 1.6.1, 8.1.5: Nebulizing is preferably done in an isolation negative pressure chamber, and if not, personnel should use an FFP2 mask. Patient should self-administer the medication and where possible, the room should not be entered within one hour after administration. Section 9.4: arterial blood gas mandatory at D1, D6 and FU Section 9.2, 9.4: if arterial blood gas is taken within 24h before first dose administration, as described in point° the arterial blood gas of screening can be used as D1 value Section 7.1.2: If a patient decides to leave hospital before day 6 of the study, for example because of clinical improvement, the oxygenation parameters at da
27 April 2020	addition site

18 May 2020	Section 9.4: Schematic overview of the data collection & interventions: lay-out was updated to improve clarity. Section 9.4: Added to flowchart, as per standard of care during follow-up visit: - 6 minutes walk test (Section 4.2) - HRCT scan to assess HRCT fibrosis score Section 10: - Clarification on study blood sampling added: EDTA only to be collected in selected sites. - processing details of samples were updated from 1500RPM or 410g to 1770 g. General: Typo's were corrected. General: "requiring invasive mechanical ventilatory support": wording "invasive" changed to "non-invasive / invasive". Section 9.2: "on page 36" added to "as described in point°". Section 9.4: clinical assessments added to flowchart: Ordinal Scale Category, Clinical Sign Sore, NEWS2 Score, SOFA Score, HScore, CURB-65, APACHE II and Glasgow Coma Scale. Section 3.2, 4.2: Mean change of SOFA score between day 1 and day 6 or between day 1 and day 11: updated to day 10. Mean change NEWS2 score between day 1 and day 6 or between day 1 and day 11: updated to day 10.
22 July 2020	PICF v 1.7 dd07-jul-2020NL PICF v1.2 dd07-jul-2020FR PICF v1.2 dd07-jul-2020ENG
19 August 2020	extension of recruitment period until 30-dec-2020 extension of recruitment number from 80 to 82
18 September 2020	extension of total study period until 30-jun-2021 extension of recruitment number from 82 to 88 (replacement of screenfailures)

15 June 2021	General: Typo's were corrected. Section 1.5 and 6.2 -patients on high dose systemic steroids (> 20 mg methylprednisolone or equivalent) Replaced by -patients on high dose systemic steroids (> 20 mg methylprednisolone or equivalent) for COVID-19 unrelated disorder AND - Patients with serum ferritin >2000 mcg/ml (which will exclude ongoing HLH) Replaced by - Patients with serum ferritin >2000 mcg/L (which will exclude ongoing HLH) Section 3.3 and Sections 4.1 and 4.2 Further clarification of Primary and Secondary endpoint measurements Section 4.3: Enumeration and description of planned pharmacodynamic measurements (biomarkers, flow cytometry, immunomonitoring) Section 9.3.6: Clarification on role of VIB-UGent Center for Inflammation Research Clarification of which pharmacodynamic parameters, biomarkers, immunomonitoring assays will be performed Definitions of follow-up visit were made consistent. Section 11: Shipment process of optional samples was updated. Section 11.3: Typo selected centres corrected to all centres Better description of sample handling and analysis by centers Secion 11.4 Clarification of sample storage and shipment, including role of VIB Section 12.3: correction statistical analysis team Further clarification on statistical analysis performed Section 13.4: Access to data and data ownership better defined Section 14.7: Period of first DSUR reporting modified to 1 year + 60 days

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported