



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 | v2 (current) |
| This version publication date | 07 April 2022 |
| First version publication date | 13 March 2022 |
| Version creation reason | • Correction of full data set correction typo's |

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 | Cormaai 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 | 24 March 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: 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® (sagramostim) 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, Aeronex 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® (sagramostim) prepared and administered intravenously
 For patients that are on a mechanical ventilator and cannot be treated

| Number of subjects in period 1 | usual care + sagramostim | 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 without reported comorbidities | 22 | 23 | 45 |
| Smoking status | | | |
| Units: Subjects | | | |
| Current | 0 | 3 | 3 |
| Former | 18 | 16 | 34 |
| Never | 22 | 22 | 44 |

| | | | |
|--|-----------------|---------------|----|
| Concomitant 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 concomitant 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 Hospitalized, 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 inter-quartile range (Q1-Q3) | 0.62 0.44 to 1.01 | 0.65 0.57 to 0.89 | - |
| Lab values - alanine aminotransferase Units: ukat/L median inter-quartile range (Q1-Q3) | 0.59 0.38 to 0.86 | 0.57 0.4 to 0.92 | - |
| Lab values - creatinine Units: micromol/L median inter-quartile range (Q1-Q3) | 75.14 68.07 to 88.4 | 78.68 68.07 to 92.82 | - |
| Biomarkers in serum - IL-6 Units: pg/mL median inter-quartile range (Q1-Q3) | 11.54 4.85 to 36.84 | 11.54 4.85 to 36.84 | - |
| Biomarkers in serum - IL-8 Units: pg/mL median inter-quartile range (Q1-Q3) | 22.51 14.14 to 32.11 | 27.44 15.91 to 46.49 | - |
| Biomarkers in serum - IL-18 Units: pg/mL median inter-quartile range (Q1-Q3) | 101.3 73.8 to 164.7 | 150.7 87.13 to 198.3 | - |
| Biomarkers in serum - C5a Units: ng/mL median inter-quartile range (Q1-Q3) | 11.18 3.91 to 16.28 | 8.83 4.52 to 16.06 | - |
| Biomarkers in serum - GM-CSF Units: fg/mL median inter-quartile range (Q1-Q3) | 9.13 7.35 to 12.42 | 9.12 6.82 to 13.39 | - |
| Biomarkers in serum - TNF Units: pg/mL median inter-quartile range (Q1-Q3) | 16.32 12.17 to 20.13 | 14.77 8.53 to 25.91 | - |
| BMI Units: kg/m ² median inter-quartile range (Q1-Q3) | 28.6 26 to 33.8 | 27.6 24.7 to 33.1 | - |
| Days since symptom onset Units: day median inter-quartile range (Q1-Q3) | 11 8.5 to 14 | 10 9 to 13 | - |
| Days since hospitalization Units: day median inter-quartile range (Q1-Q3) | 3 2.5 to 4.5 | 3 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 without reported comorbidities | 45 | | |
| Smoking status | | | |
| Units: Subjects | | | |
| Current | 3 | | |
| Former | 34 | | |
| Never | 44 | | |
| Concomitant medication at randomization | | | |
| Units: Subjects | | | |
| Glucocorticoids | 20 | | |
| Antiviral drugs (remdesivir) | 3 | | |
| Hydroxychloroquine | 50 | | |
| Antibiotics | 3 | | |
| Patients without reported concomitant medication | 5 | | |
| 6-category ordinal scale | | | |
| Units: Subjects | | | |

| | | | |
|--|-------------------------|--|--|
| 5 Hospitalized, no supplemental oxygen | 4 | | |
| 4 Hospitalized, supplemental oxygen | 71 | | |
| 3 Hospitalized, NIMV or HFOD | 6 | | |
| Lab values - C-reactive protein Units: mg/L median inter-quartile range (Q1-Q3) | 74.5 38.75 to 147.45 | | |
| Biomarkers in serum - IL1RA Units: ng/mL median inter-quartile range (Q1-Q3) | 1162 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 inter-quartile range (Q1-Q3) | 0.02 0 to 0.1 | | |
| Lab values - lymphocyte count Units: x 10 ⁹ /L median inter-quartile range (Q1-Q3) | 1 0.7 to 1.3 | | |
| Lab values - ferritin Units: mcg/L median inter-quartile range (Q1-Q3) | 721 425 to 1068 | | |
| Lab values - D-dimer Units: nmol/L median inter-quartile range (Q1-Q3) | 3.81 2.79 to 5.31 | | |
| Lab values - lactate dehydrogenase Units: ukat/L median inter-quartile range (Q1-Q3) | 5.26 4.21 to 6.68 | | |
| Lab values - aspartate aminotransferase Units: ukat/L median inter-quartile range (Q1-Q3) | 0.65 0.48 to 0.95 | | |
| Lab values - alanine aminotransferase Units: ukat/L median inter-quartile range (Q1-Q3) | 0.58 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 until follow up

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|-----|
| Dictionary version | 5.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | usual care |
|-----------------------|------------|

Reporting group description: -

| | |
|-----------------------|---------------------------|
| Reporting group title | usual care + sargramostim |
|-----------------------|---------------------------|

Reporting group description: -

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 30 March 2020 | correction inclusion criteria to PaO ₂ /FiO ₂ below 350 |
| 17 April 2020 | <p>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.</p> <p>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</p> <p>Section 10: redefining sampling.due to addition of extra study sites.</p> <p>Section 8.1.5: better definition of duration of treatment</p> <p>Section 13.6: Despite the known safety profile of the study medications and study design, a DSMB is foreseen.</p> <p>General: Better definition of progressive disease: Progression to ARDS requiring mechanical ventilation is removed and replaced by: progressive disease requiring mechanical ventilatory support.</p> <p>General: Safety follow-up period is 10-20 weeks.</p> <p>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.</p> <p>Section 9.4: arterial blood gas mandatory at D1, D6 and FU</p> <p>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</p> <p>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</p> |
| 27 April 2020 | addition site |

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|-------------------|---|
| 18 May 2020 | <p>Section 9.4: Schematic overview of the data collection & interventions: lay-out was updated to improve clarity.</p> <p>Section 9.4: Added to flowchart, as per standard of care during follow-up visit:</p> <ul style="list-style-type: none"> - 6 minutes walk test (Section 4.2) - HRCT scan to assess HRCT fibrosis score <p>Section 10:</p> <ul style="list-style-type: none"> - 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. <p>General: Typo's were corrected.</p> <p>General: "requiring invasive mechanical ventilatory support": wording "invasive" changed to "non-invasive / invasive".</p> <p>Section 9.2: "on page 36" added to "as described in point°".</p> <p>Section 9.4: clinical assessments added to flowchart:</p> <p>Ordinal Scale Category, Clinical Sign Sore, NEWS2 Score, SOFA Score, HScore, CURB-65, APACHE II and Glasgow Coma Scale.</p> <p>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.</p> <p>Mean change NEWS2 score between day 1 and day 6 or between day 1 and day 11: updated to day 10.</p> |
| 22 July 2020 | <p>PICF v 1.7 dd07-jul-2020NL</p> <p>PICF v1.2 dd07-jul-2020FR</p> <p>PICF v1.2 dd07-jul-2020ENG</p> |
| 19 August 2020 | <p>extension of recruitment period until 30-dec-2020</p> <p>extension of recruitment number from 80 to 82</p> |
| 18 September 2020 | <p>extension of total study period until 30-jun-2021</p> <p>extension of recruitment number from 82 to 88 (replacement of screenfailures)</p> |

| | |
|--------------|---|
| 15 June 2021 | <p>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</p> <p>AND</p> <p>- 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</p> <p>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 Section 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</p> |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported